FUNDAMENTALS OF CLINICAL REPRODUCTIVE ENDOCRINOLOGY

Edited by
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Contents

List of contributors, iv
Forward, vii
Preface , viii
Dedication, ix
Acknowledgements, xi

Section A General Endocrinology

1. Introduction and Overview of Reproductive Endocrinology 2
2. Endocrine basis of Sexual Differentiation/Development and Intersexuality 11
3. Endocrinology of Puberty and Adolescence 18
4. Endocrinology of Menstruation and the Menstrual Cycle 29
5. The Endocrinology of Menopause 35
6. Reproductive Endocrine Aspects of Contraception 52
7. Hormone Assay in Reproductive Endocrinology 73
8. Endocrinology of Anorexia Nervosa and Other weight related disorders 88
9. Endocrinology Changes with variation in Body Mass Index (BMI) and Metabolism 98
10. Thyroid Function and Disease in Females 112

Section B Gynecologic Endocrinology

11. Endocrinology of polycystic ovary syndrome 122
12. The Endocrinology of Reproductive Cancers 131
13. Endocrinology of Premenstrual Syndrome (PMS) and Idiopathic Edema 154
14. Endocrinology of Endometriosis 169
15. Endocrinology of Uterine Fibroids 177
16. Ovarian Insufficiency 184
17. Endocrinology of Recurrent Miscarriages 191
18. Endocrinology of Ectopic Pregnancy 205
19. Endocrinology of Hirsutism and Virilization in Women 216

Section C Obstetric Endocrinology

20. Endocrinology of Normal Pregnancy 235
21. Placental Endocrinology 247
22. Endocrinology of Labour 260
23. Endocrinology of lactation and the puerperium 265
24. Understanding and Managing Pregnancy in Women with Diabetes Mellitus 269

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Forward

It is my pleasure and singular honor to write this foreword for a book on a very important subject in Obstetrics and Gynecology – ***Fundamentals of Clinical Reproductive Endocrinology***. This timely publication is perhaps the first from this region by 35 Authors whose scholarship is embodied in the depth of information on Clinical Endocrinology crafted in a lucid and easy to digest manner.

Reproductive Endocrinology is a subset of Obstetrics and Gynecology and this book focus on the most common reproductive endocrine conditions encountered by healthcare providers. The authors draw their references from wide range of research publications pertaining to the fundamental practice of Obstetrics and Gynecology as presented in the three sections of the book.

Section A aptly describes general endocrinology providing information on complex endocrine basis of sexual differentiations, onset of puberty and Adolescence, Hormonal interaction between the hypothalamus, anterior pituitary gland and ovaries that regulate the female reproductive system and the hormone profile at menopause. Abnormal Uterine bleeding and amenorrhea are frequent presentation that require understanding of endocrine pathways that will influence clinical management. The Endocrinology of Anorexia nervosa and other weight related disorders make very interesting reading for every medical practitioner who may be faced with emerging cases of overweight and menstrual disorders.

In a continent characterized by areas of high fertility and infertility belt, most of the chapters will be relevant to Gynecologists seeing infertility patients while the chapter on Contraception will be of interest to those interested in fertility management. Expanding methods and choices by introducing new methods of family planning will meet the needs of people from diverse socio-cultural background and assist Government to moderate the high population growth.

Section B focuses on the most common reproductive endocrine conditions encountered by healthcare practitioners e.g. Polycystic ovary syndrome, Ovarian insufficiency, Recurrent miscarriages, Ectopic pregnancy, Hirsutism and virilisation in women, Endometriosis and Endocrinology of Reproductive cancers.

Section C captures endocrinology of normal pregnancy, placental steroid production, labor, lactation and puerperium. Of interest is the detailed description of Diabetes Mellitus and management of Gestational Diabetes Mellitus that is the commonest endocrine disorder and medical complication of pregnancy, with associated feto-maternal mortality and morbidity if not diagnosed and managed appropriately.

In general, the authors' aim is to advance knowledge and practice in our field while providing patients with the highest level of care. Therefore, this book is a must read for anyone whose career is in the field of Obstetrics and Gynecology in particular those managing patients with reproductive failure and Endocrinologists. Undergraduates and graduate students will benefit intellectually from the lucidly written 24 chapters.

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Preface

Reproductive endocrinology is a sub-specialty of Obstetrics and Gynecology that deals with reproductive medicine and addresses hormonal function as it pertains to reproduction as well as the issue of infertility and reproductive disorders. Endocrinology is a very complex subject, particularly regarding the interpretation of interplay of hormones which needs detailed information about the basic physiology and clinical relevance. Reproductive Endocrinology looks not only at the obstetric and gynecological problems in the context of endocrine diseases, but also studies family planning and prospects for normal development and differentiation of the fetus including aberrations that may occur, as well as andrologic profile as it pertains to infertility. The importance of reproductive endocrinology cannot therefore be over emphasized as having a firm grasp and understanding of the concepts will assist the reproductive endocrinologist in the management of patients who present at the gynecological and obstetric clinics with a wide spectrum of various conditions involving the female reproductive system as well as pregnancies complicated by endocrine dysfunction.

This subject is scarcely grasped and appreciated by both students, residents and practicing doctors making the management of reproductive endocrine clinical entities quite a herculean public health challenge. Yet the clinical entities of Reproductive Endocrinology and Infertility constitute a significant proportion of the work load of practicing Gynecologists and healthcare providers globally and in the West African sub-region in particular. Certainly, there is paucity of capacity for investigation and treatment of these entities in the West Africa sub-Region. Worst still the availability of indigenous resource materials and textbooks focusing exclusively on these subject matters and the broader subspecialty is lacking. It is against this background that this textbook was conceptualized to complement our earlier published textbook of *Infertility and Assisted Conception in the Tropics*. It is written in a systematic manner that makes it an excellent piece for training of both undergraduate medical students and postgraduate resident doctors and endocrinologist.

This book, *Fundamentals of Clinical Reproductive Endocrinology,* is a compelling testament and should appeal to both those who have already submersed themselves in the specialty of Infertility and Reproductive Endocrinology, practicing Obstetrician & Gynecologists and new-comers to the area including medical students, resident doctors in Obstetrics and Gynecology as well as general medical practitioners involved with infertility care in the tropics as well reproductive endocrine disorders.

Essentially, the chapters in this book are organized into three sections. The first section has ten chapters on general endocrinology. The second section is made up of nine chapters on Gynecologic endocrinology, while the third section has five chapters on obstetric endocrinology.

Certainly, from the outlay of the book and the topics therein, in-depth understanding is required to deal with this broad range of topics. Fortunately, I was again availed of the time and expertize of distinguished array of international scholars as contributors, whose knowledge, experience and opinions are invaluable, particularly in the area where studies are scant and good quality evidence hard to find.

Overall, this book will improve the management of reproductive endocrine disorders, infertility and help build the capacity of practitioners in these regions, in addressing critical issues in the discipline. Programmers, academicians and scholars, as well as all practitioners of infertility and reproductive endocrinology, gynecology and reproductive health in sub-Saharan Africa and across the world will find this book of considerable interest and value. The book has been written in an easy to read format and therefore also a reference material for a wide reading audience including undergraduate and postgraduate students in obstetrics & gynecology, practicing gynecologists, general medical physicians, community physicians, nurses and midwives, and reproductive health practitioners. This book will surely make significant contribution to the practice of Reproductive Endocrinology in the coming years.

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Dedication

This book is dedicated first and foremost to the almighty God who gave the vision and strength that brought the work to a successful completion. And to my dear and amiable Parents – Chief Lawrence E. Aghoja and Mrs. Mary F. Aghoja. They committed their all in ensuring I had a very sound education and raised me in the finest tradition of hard work, commitment to duty, integrity, honesty, discipline and reverence for God. I thank the Almighty and Most High God for giving them life and health to witness my rise to the pinnacle of the respective professions of Medicine and Academia. And I wish them the very best of God's choicest blessings and profound health of mind and body in the coming years.

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Many thanks to my Jewel of inestimable value – Vivian and my great kids – Eguono, Vwede, Jite & Nuvie for tolerating my time away in writing and editing, to my colleagues Oliver and Preye with whom this work was initially conceptualized, and the DERHIREC team led by Emmanuel Rotimi who worked arduously with me to see to the completion of this masterpiece.

Section A

General Endocrinology

Reproductive Endocrine Aspects of Contraception

Omokanye LO, Awo O, Panti AA, Balogun OR

INTRODUCTION

The term contraception includes all measures, temporary or permanent, designed to prevent pregnancy due to the act of coitus. Currently there is a pressing need for limiting the family size at personal level and for the control of population at a national level. The need of birth control at personal level has arisen through increased cost of living, scarcity of accommodation, a desire for better education of children in the current competitive world and a desire for an improved standard of living[1]. Rapid population growth is a critical issue in most developing countries. In developing countries, women continue to die because they lack access to contraception. Each pregnancy multiplies a woman's chance of dying from complications of pregnancy or childbirth. Maternal mortality rates are particularly high for young and poor women, those who have least access to contraceptive services. It is estimated that one in three deaths related to pregnancy and childbirth could be avoided if all women had access to contraceptive services[2]. Expanding access to client-centred information and services, where a range of effective contraceptive methods is offered and responsive counselling provided, reduces the number of unplanned pregnancies. These unintended pregnancies often lead to sub-optimal pregnancy care, unsafe abortions and overwhelmed mothers. As many as 50% of pregnancies are unplanned, and 25% are unwanted. The unwanted pregnancies are disproportionately high among young, unmarried girls who often lack access to contraception[2-5].

More than one quarter of pregnancies worldwide, about 52 million annually, end in abortions. Many of these procedures are clandestine, performed under unsafe conditions. About 13 per cent of maternal deaths are attributed to unsafe abortions, coupled with lack of skilled follow-up. Some 47,000 women each year die as a result. The high level of unmet need for quality contraceptive services and the corresponding number of unintended pregnancies is a key reason why so many seek out abortions. Young women are especially vulnerable. The decision of when or even whether to have children is a basic human right[3].

Increase in family size and increases in the population of communities, nations, regions, and the world at large are associated with serious medical and socioeconomic implications. Thus contraception merits consideration not only by health workers but also professionals in other areas of public service. This chapter reviews the various methods of contraception with emphasis to hormonal contraception.

METHODS OF CONTRACEPTION

Contraception may be either temporary or permanent. The various methods are as shown in Table 1.

Temporary Contraception: This are methods commonly used to postpone or to space births.

Permanent Contraception: This is often referred to as sterilization.

Emergency Contraception: This is the use of a drug or device as an emergency mea-sure to prevent pregnancy after coitus.

Table 1: Methods of Contraception.

Temporary methods	Natural methods
	Barrier methods
	Intrauterine contraceptive devices
	Hormonal contraceptives
Permanent methods	Female Tubal occlusion
	Male: vasectomy
Emergency contraception	Hormonal methods
	Non hormonal methods

Contraceptive Effectiveness

The Effectiveness of a contraceptive method is determined by the Pregnancy rate per hundred years (HWR) of use. This is calculated using the following formula (pearl index):

Pregnancy failure Rate/HWR =

$$\frac{\text{Number of accidental pregnancies} \times 1200}{\text{Clients observed x months of Exposure}}$$

Note: 1200 = Number of months in 100 years.

Example: if 50 couples have used a method for 1 year and have resulted in 10 Pregnancies, the pregnancy rate is calculated to be:

$$\frac{10 \times 1200}{50 \times 12} = 20$$

When the pregnancy rate is below 10, the effectiveness of the method is high. If it is more than 20, it is said to be low.

The pregnancy rate in a population that does not use contraception is about 80 per hundred woman years.

The Effectiveness of a contraception is defined by its theoretical effectiveness and its use effectiveness.

Theoretical Effectiveness: is the antifertility action of any contraceptive method under ideal conditions with no omissions or errors in use.

Use - Effectiveness or Actual Effectiveness: is the protection achieved under realistic conditions of life.

No ideal contraceptive is currently available. The characteristics of a perfect contraceptive include effectiveness, safety, low cost, ease of use, lack of relation to coitus, and absence of the requirement for repeated motivation. However, only methods with endocrine basis shall be discussed.

Temporary Contraceptive Methods

These can be grouped into:

- Natural Methods
- Morden Methods

IMPORTANT NATURAL CONTRACEPTIVE METHODS

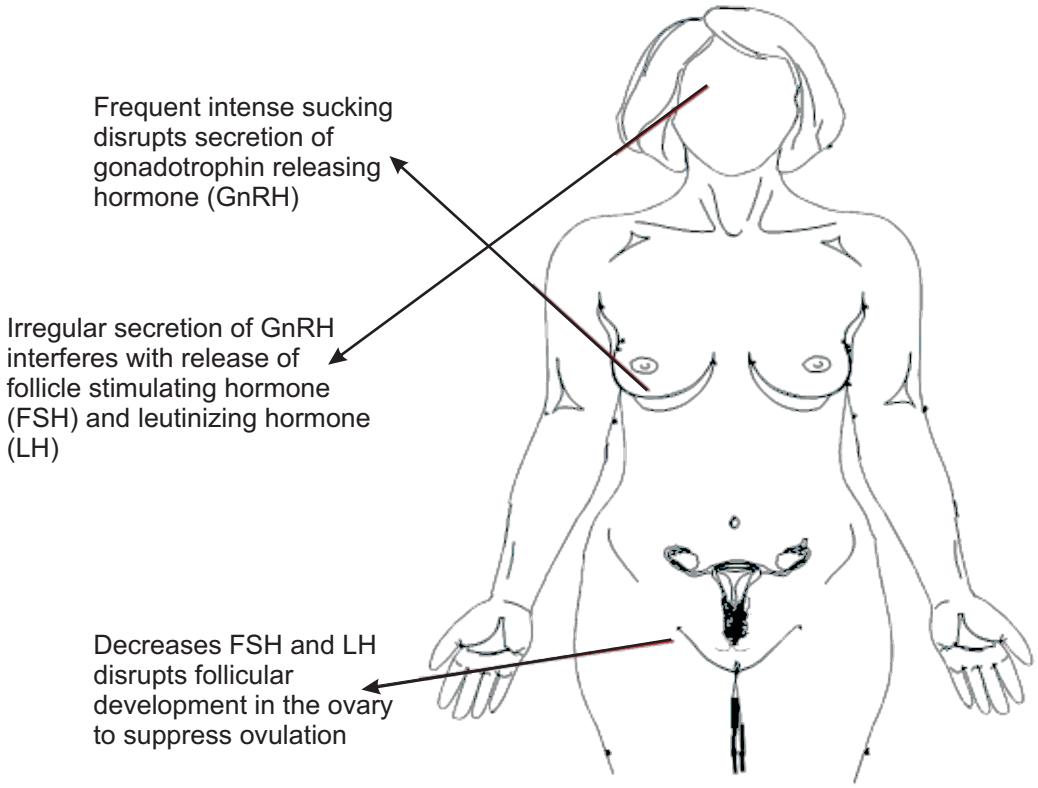
- **Lactational Amenorrhoea Method (LAM)**
- **Cortus Intemptus**
- **Rhythm Method**

Lactational Amenorrhoea Method (LAM): Prolonged and sustained breastfeeding offers a natural protection against pregnancy. This method is more effective in women who are amenorrheic than those who are menstruating. The risk of pregnancy to a woman who is exclusively or almost exclusively breastfeeding and amenorrhoeic is less than 2% in the first 6 month[4]. The delay of ovulation postpartum is highly variable and ovulation has been known to

occur early during breast-feeding. The advantages of this method are its lack of cost and ready availability.

Elevated levels of prolactin during breast feeding inhibits the pulsatile secretion of GNRH. Prolactin excess has short loop positive feedback effects on dopamine. Increased dopamine reduces GNRH by suppressing arcuate nucleus function, perhaps in a mechanism mediated by endogenous opioid activity[6]. The exact mechanism for the suppression of GNRH secretion remains to be unravelled. The importance of GNRH suppression by prolactin is reinforced by the demonstration that treatment of amenorrhoeic, lactating women with pulsatile GNRH fully restores pituitary secretion and normal ovarian cyclic activity [6]. Prolactin concentrations are increased in response to the repeated suckling stimulus of breastfeeding. Under this condition FSH and LH concentrations are low. The low levels of gonadotropins do not allow the ovary during Lactational hyperprolactinemia to display follicular development and secrete oestrogen. Therefore, vaginal dryness and dyspareunia are commonly reported by breastfeeding women [6].

Figure 1: Shows The Endocrine Basis of LAM.



LAM: Mechanisms of Action

RYTHM METHOD

The rhythm method depends upon the avoidance of sexual intercourse around ovulation. in a 28 day cycle, ovulation normally occurs on the 14th day of the cycle but may occur any time between the 12th and 16th day. spermatozoa deposited in the female genital tract may survive for 24 hours. the ovum itself may live for 12 to 24 hours so that intercourse between the 11th and 17th day may result in a pregnancy. the safe period is therefore, calculated from the first day of the menstrual period until the 10th day

of the cycle and from the 18th to the 28th day. an alternative method is to calculate the risk period, which is from three day before ovulation to three day after ovulation. in a 35 day menstrual cycle, therefore ovulation will occur on the 21st day so that the risk period is from day 18 to 24[1]. A clinically useful method of predicting ovulation that is independent of the length of the cycle is based on measurements of viscosity of cervical mucus. The properties of the cervical mucus change under the influence of the ovarian hormones on different days of the menstrual cycles. oestrogen increases the water and electrolyte content with decrease in protein. as such, the mucus becomes copious, clear and thin. progesterone, on the other hand, decreases the water and electrolytes but increases the protein. as a result, the mucus becomes scanty, thick and tenacious. during the mid-cycle, the cervical mucus is increased in elasticity (spinnbarkeit phenomenon) due to oestrogen level. after ovulation when corpus luteum forms , progesterone is secreted. under its action, the cervical mucus loses its property of elasticity. this loss of elasticity after its presence earlier is an indirect evidence of ovulation[5]. intercourse is considered safe during the dry days of the mucus until after the menses when mucus will be detected again.

Rhythm or calendar methods of predicting ovulation are dependent upon length of the prior cycle. Thus historic data are needed to predict satisfactorily a future ovulation. The success of the method depends upon the regularity of the menstrual cycle and requires strong motivation. For maximal safety long periods of abstinence are required. Although menstruation occurs quite regularly at 14days after ovulation the length of the pre-ovulatory phase is quite variable. A rise in basal body temperature BBT of about 0.5^0C during the luteal phase of the cycle can be used to detect ovulation but it is necessarily a retrospective finding since it is based on a basal temperature rise which is due to the effect of progesterone which is known to exert a thermogenic effect on the body. however progesterone is produced after ovulation by the corpus luteum. The failure rate of this method is 20 - 30 hundred woman years. (Table 2)

MODERN METHODS

Intrauterine Contraceptive Devices (IUCD):

The intrauterine device is used world-wide by over 100 million women[6] . IUCD is an effective, reversible and long term method of contraception, which does not require replacement for long periods and does not interfere with sexual activity. The device is impregnated with barium sulphate to render it radiopaque, so that it can be detected by radiography. Each device has a nylon thread attached to its lower end and this thread protrudes through the cervical canal into the vagina, where it can be felt by the patient and the doctor. IUCD has undergone a lot of development, from the first generation of non-medicated devices to the recent progestogen impregnated devices.

Table 2. Rhythm method.

Advantages
No cost
No systematic side effect
Disadvantages
High failure
Need training to use the method
Difficulty on calculating safe period
Abstinence from sex during unsafe periods
Not suitable for clients with irregular

First Generation IUCDs

These generations of IUCDs are biologically inert devices that include Lippes loop, Dalkon shield and Saf-T-coil. They can be left in situ for several years. The Lippes loop was more popular. It comes in four different sizes and open intrauterine devices. Because of its large size; abdominal cramps, menorrhagia and perforations of the uterus lead to diminished tolerance and withdrawal from market in most countries[6,7]. However, it is used in clinical practice in the management of uterine synechiae.

Second Generations IUCDs

These generations of IUCDs witnessed medical impregnation of the devices. These include copper T 200, copper 7 multiload, multiload copper 250, copper T 220, and Nova T amongst others . Copper carrying devices had copper wire wrapped round the stem of a polypropylene frame. The widely used copper T 200 carries 200sqmm surface area of copper wire round the vertical stem of the device. The device contains 120mg of copper. The copper is lost at the rate of 50ug per 24 hours and is removed after 3 years[6]. Improvements on this generation gave birth to the third generation IUCD

Third Generation IUCDs

These generations of IUCDs are just like the second generation IUCDs but the major difference is the addition of copper wire on the vertical stem of the T shaped device to increase the quantity of copper on it and thereby increasing its duration of action. These includes copper T 380A, multiload 375, copper safe 300, and copper-fix 330. the copper 330A contains 380sqmm of copper round the frame i.e. 314sqmm on the stem and 33sqmm of copper on each horizontal arms. These are usually replaced every 10 years [6].

Fourth Generation IUCDs

These generation of IUCDs are impregnated with hormones like progestogens or levonorgestrel[5] . Examples of these are progestasert, levonova, and mirena respectively. Progestasert is a T-shaped device carrying 38mg of progesterone in silicon oil reservoir in the vertical stem. It releases 65ug of the hormone per day. The progestasert has its own special method of insertion without a plunger which makes the insertion more difficult. This requires yearly replacement[5]. It is however no longer manufactured for economic reasons[5]. Levonova contains 60mg of levonor gesstrel and releases the hormone in very low doses of 20ug/day. It lasts for 5 years[6].

Mirena is 'T'shaped device, with polydimethyl silicon membrane around the stem which acts as a steroid reservoir. total amount of levonor gestrel at the rate is 52mg and is released at the rate 20ug/ day[5]. This device is to be replaced every 5 years. Its efficacy is comparable to sterilization [5]. It acts by inducing strong and uniform suppression of the endometrium. Cervical mucus becomes scanty. anovulation and insufficient luteal phase has also been mentioned. serum progesterone level is not increased[5,6]. It also has many non-contraceptive benefits which are highlighted in page 12.

Mechanisms of Action of IUCDs

Several mechanisms are responsible for the contraceptive effects of an IUCD.

1. The presence of a foreign body in the uterine cavity renders the migration of spermatozoa difficult [6]
2. A foreign body within the uterus

provokes uterine contractility, and increases the tubal peristalsis which results in quick migration of fertilised ovum into the uterine cavity before the endometrium is receptive[5].

3. The device in situ causes nonspecific inflammatory reactions along with biochemical reactions in the endometrium causing leucocytic infiltrations in the endometrium. The macrophages engulf the fertilized egg if it enters the endometrium tissue[1].
4. The copper device eludes ionised copper which brings about enzymatic and metabolic changes in the endometrial tissue which are inimical to the implantation of the fertilized ovum[8].
5. Progesterone releasing IUDs add the endometrial action of the progestin to the foreign body reaction. The endometrium becomes decidualized with atrophy of the glands, it also causes alteration in the cervical mucus which prevents penetration of sperm. It also prevents ovulation[6].

Table 3: IUCDs - Advantages And Disadvantages

Advantages

i. It is coital independent
ii. Prolonged contraceptive protection
iii. No systemic side effects
iv. Simplicity in the insertion technique reversibility to fertility is prompt after removal

Disadvantages

i. Require motivation
ii. Adverse local reactions manifested by menstrual abnormalities, PID, pelvic pain and menorrhagia
iii. Hormone releasing IUDs are expensive
iv. Risk of ectopic pregnancy

Figure 2: Generations of IUCD

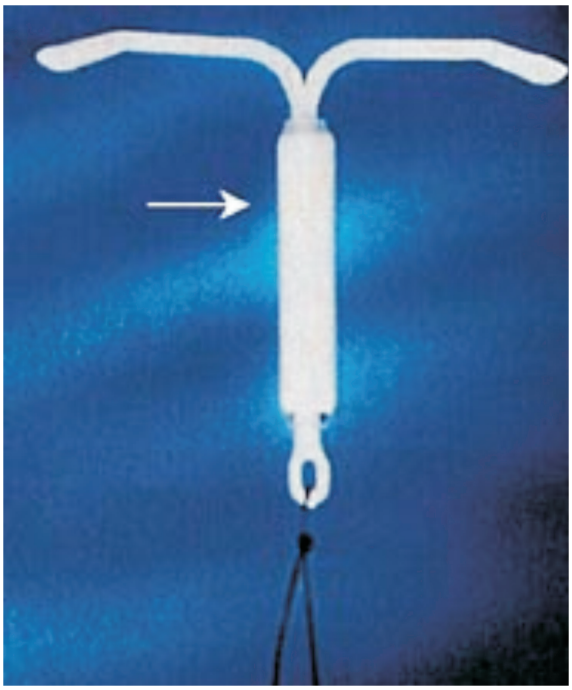


First generation I.U.C.D. is **Lipes loop**

Second generation I.U.C.D. is **Copper T-200**

Third generation I.U.C.D. is **Gyne-T 380** with 4 years Intra uterine life

Figure 3: Levonorgestrel



Fourth generation

Levonorgestrel
I.U.D. 20

A capsule on the Stem contain mixture of silicon rubber & 60mg of Progestron (Levonorgestril) Developed by steroid research Laboratory-Finland Levonorgestrel, 60mg releasing 20mcg per day estimated to last 7 years.

Contraindications

The World Health Organization (WHO) has developed a list of absolute and relative contra-indications to use of an IUD [9].

Absolute Contraindications

1. Pregnancy
2. Pelvic inflammatory disease (PID) or sexually transmitted infection (STI)
3. Puerperal sepsis
4. Immediate post-septic abortion
5. Severely distorted uterine cavity
6. Unexplained vaginal bleeding
7. Cervical or endometrial cancer
8. Malignant trophoblastic disease
9. Copper allergy (for copper IUDs)
10. Breast cancer (for LNG-IUS)

Relative Contraindications

1. Risk factor for STIs or human immunodeficiency virus (HIV)
2. Impaired response to infection in HIV positive women and women undergoing corticosteroid therapy from 48 hours to 4 weeks postpartum
3. Ovarian cancer
4. Benign gestational trophoblastic disease

Non Contraceptive Benefits

1. Case-control studies provide some evidence that use of non-medicated or copper IUDs reduces the risk of endometrial cancer [6]. This protective effect is not related to the duration or timing of use and its mechanism is not well understood.
2. Menorrhagia responds favorably to use of the LNG-IUS, with reported reductions in

menstrual blood loss of 74 to 97% and favorable effects on haemoglobin levels [10]. In two studies of women scheduled to undergo hysterectomy for menorrhagia, 64 to 80% of women randomized preoperatively to LNG-IUS insertion subsequently cancelled their hysterectomy, compared with 9 to 14% of women randomized to receive other medical treatments [11].

3. Dysmenorrhea may also improve in LNG-IUS users[6].
4. A randomized controlled study found that use of the lng-ius protects against endometrial hyperplasia and polyps in women on tamoxifen or postmenopausal oestrogen therapy[12].
5. Small reports support a beneficial effect in the treatment of fibroid-related menorrhagia [13].
6. In a randomised, 5 year trial comparing copper IUD with the LNG-IUS, pelvic infection was lower than the incidence in a general population with both devices, but the rate with the LNG-IUS was significantly lower compared with the copper IUD [14].
7. The LNG-IUS has been used successfully to treat endometriosis, and especially pelvic pain and dysmenorrhoea associated with endometriosis[15].

HORMONAL CONTRACEPTION

Hormonal contraception is one of the most effective contraceptive methods available[5]. A wide variety of hormonal preparations are available for contraceptive use. The mode of action depends upon the hormones used, the mode of delivery and the time of administration. Table 4 shows various forms of hormonal contraceptives.

Table 4: Hormonal contraception

Oral	Combined preparations
	Single preparations (mini pills)
Parental	Injectable
Device	IUD (LNG-IUS)
	Implants
	Vaginal ring
	Transdermal patches

ORAL HORMONAL CONTRACEPTIVES

Oral contraceptives are one of the most common means of contraception throughout the world [1]. It has become the most used pharmacological agent since it was first marketed in 1960.

The Combined Oral Contraceptive Pills (Combined OCPs)

The combined oral pill was first introduced in 1960 [1]. It has undergone several modifications over the years. Combined oral pills contain a mixture of two hormones estrogen and progesterone. Two types of estrogen are used in combined OCs: ethinyl estradiol and mestranol[6]. Mestranol is a "prodrug" that is converted *in vivo* to ethinyl estradiol [6]. The estrogen content of the pill is of major importance. thrombosis is one of the increased risk of death (in the past with high doses) from a variety of circulatory problems. this side effects is related to oestrogen, and it is dose related. therefore, the dose of estrogen is a critical issue in selecting an oral contraceptives[6]. however, the newer pills now contain low dose of the oestrogen ie products containing less than 50 ug of ethinyl estradiol. Several different

progestins, of varying degrees of progestational potency, are used in combined OCs. The progestins may also have estrogenic, antiestrogenic, or androgenic activity. Progestins can be classified according to their chemical structure as an: Estrane (norethindrone, ethyno-diol diacetate) or as a: Gonane (levonorgestrel, desogestrel, norgestimate). In general, the gonane progestins appear to be more potent than the estrane derivatives (smaller doses can be used), but otherwise differences between the estrane and gonane compounds are difficult to characterize.

Progestins have also been classified according to the sequence of their development (first, second, or third generation), but the definitions of first, second, or third generation progestins are not universally accepted. Newer progestins (norgestimate, desogestrel and drospirenone) have been shown to have little or no androgenic activity .

Formulations may be :

1. Monophasic (each tablet contains a fixed amount of estrogen and progestin);
2. Biphasic (each tablet contains a fixed amount of estrogen, while the amount of progestin increases in the second half of the cycle); or
3. Triphasic (the amount of estrogen may be fixed or variable, while the amount of progestin increases in 3 equal phases).

Biphasic and triphasic formulations were initially developed with the intent of lowering the total steroid content of combined oral contraceptive pills.

Mechanisms of Action

The combined OCP's has multiple mechanisms of action and these may contribute to its high efficacy. Its main mechanism action is to suppress gonadotropin secretion via an effect on both the pituitary and hypothalamus, thereby inhibiting ovulation. the progestational agent in the pill primarily suppress LH secretion (and thus prevents ovulation) while the oestrogenic agent suppress FSH secretion (and thus prevents emergence of a dominant follicle). therefore, the oestrogenic component significantly contributes to the contraceptive efficacy. however if follicular growth and development were not sufficiently inhibited, the progestational component would prevent the surge like release of LH necessary for ovulation [6]. the oestrogen in the pill serves two other purposes. it provides stability to the endometrium so that irregular shedding and unwanted breakthrough bleeding can be minimized and the presence of oestrogen is required to potentiate the action of the progestational agents.

Other mechanisms of action include:

1. Development of endometrial atrophy, thereby making the endometrium unreceptive to implantation[5]
2. Production of viscous cervical mucus that impedes sperm transport[1].
3. Possible effect on secretion and peristalsis within the fallopian tube, which interferes with ovum and sperm transport [6].

Efficacy of Combined OCPs

The combined OCPs are highly effective method of reversible contraception. With perfect use, the combined OC is 99.9% effective in preventing pregnancy [6] However, typical user failure rates range from 3 - 8%[5]. Poor patient compliance is a major factor in limiting effectiveness.

Indications

It is particularly suited for women who wish to

take advantage of its non-contraceptive benefits. The use of condoms is still recommended in combined OCP users for protection against sexually transmitted infections (STIs) and human immunodeficiency virus (HIV).

Non - Contraceptive Benefits

The non-contraceptive incidental benefits can be listed as follows

1. Effective contraception (less need for induced abortion, less need for surgical sterilization)
2. Less endometrial cancer
3. Less ovarian cancer
4. Less colorectal cancer
5. Fewer ectopic pregnancies
6. More regular menses (less flow, less dysmenorrhoea, less anaemia.)
7. Less salpingitis
8. Less benign breast disease
9. Increased bone density
10. Probably less endometriosis
11. Possibly less rheumatoid arthritis
12. Possibly protection against atherosclerosis
13. Possibly fewer fibroids
14. Possibly fewer ovarian cysts

Oral contraceptives are frequently utilized to manage the following problems and disorders:

Definitely Beneficial

1. Dysfunctional uterine bleeding
2. Dysmenorrhoea
3. Mittelschmerz
4. Endometriosis prophylaxis
5. Acne and hirsutism
6. Hormone therapy for hypothalamic amenorrhoea
7. Prevention of menstrual porphyria
8. Control of bleeding (dyscrasias, anovulation)

Possibly Beneficial

1. Functional ovarian cysts
2. Premenstrual syndrome

Contraindications

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to the use of combined OCs, based on the available evidence of risks [16].

The non-contraceptive benefits of oral contra-ception can be grouped into two main categories: benefits that incidentally accrue when oral contraception is specifically utilized for contraceptive purposes and benefits that result from the use of oral contraceptives to treat problems and disorders [5,6].

Table 5: Contraindications of Oral Contraceptives

Absolute Contraindications

i. Less than 6 weeks postpartum if breastfeeding
ii. Smoker over the age of 35 (=15 cigarettes per day.
iii. Hypertenson (systolic = 160mm Hg or diastolic = 100mm Hg
iv Current or past history of venous thromboembolism (VTE)
v. Ischemic heart disease
vi. History of cerebrovascular accident
vii. Complicated valvular heart disease
viii. Migraine headache with focal neurological symptoms
ix. Breast cancer (current)
x. Diabetes with retinopathy/nepthrpathy/ neuropathy
xi. Severe cirrhosis

xii. Liver tumor (adenoma or hepatoma)

Relative Contraindication

I. Smoker over the age of 35 (<15 cigarette per day
ii. Adequate controlled hypertension
iii. Hypertension (systolic 140-159mm Hg, diastolic 90-99mm Hg)
iv. Migraine headache over the age of 35
v. Currently symptomatic gallbladder disease
vi. Mild cirrhosis
vii. History of combined OCP-related cholestasis
viii. Users of medications that may interfere with combined OCP metabolism eg carbamazepine, nevirapine, rifampicin amongst others.

Side Effects

Some combined OC users will experience minor side-effects, most commonly during the first 3 cycles. These side-effects may lead to discontinuation of the combined OC.

Reassurance and adequate counselling about expected common side-effects can help to prevent unnecessary discontinuation and enhance compliance.

The most common reason patients discontinue combined OC use is:

1. Abnormal menstrual bleeding
2. Nausea,
3. Weight gain,
4. Mood changes,
5. Breast tenderness, and
6. Headache.

Initiation

Patient Assessment

Before prescribing a combined OC, a thorough history should be taken, including potential contraindications, smoking history, and medications.

The physical examination should include a blood pressure measurement. A pelvic examination, although an important aspect of well-woman care, is not mandatory before providing combined OCPs. The pelvic examination may be postponed until a follow-up visit. No routine laboratory screening is required. Routine screening for thrombophilias is not recommended.

Counselling

Adequate counselling prior to initiation of combined OCs may help to improve compliance (regular use) and adherence (continuation). Counselling should include the following:

1. Instructions on how to take the combined OC
2. Information on potential side-effects
3. Non-contraceptive benefits of the combined OC
4. Addressing common myths and misconceptions
5. Discussing risks and warning signs, including when to seek medical care
6. Discussing what to do if pills are missed
7. Emphasizing dual protection (the combined OC with condom use to prevent STIs and HIV infection)
8. Information about emergency contraception in the event of missed pills

Prescription

The choice of a combined OC, for first-time users, should take into account the: prescriber's clinical judgment and the preferences of the user. A low-dose preparation (≤ 35 µg of ethinyl estradiol) is preferred. The preparation of choice for the combined OC user is the one that provides:

1. Effective contraception,
2. Acceptable cycle control, and

3. The least side-effects.
4. Various start dates for the combined OC are used.
5. Conventionally, the combined OC is started during the first 5 days of the menstrual cycle.

If the combined OC is started within the first 5 days of the menstrual cycle, a backup method of contraception is not necessary for prevention of pregnancy, provided that no pills have been missed.

Another alternative is the Quick Start method, where a combined OC user takes her first pill in the health-care provider's office after ruling out pregnancy.

A back-up method of contraception should be used for the first week after combined OC initiation if the Quick Start method is used.

The Quick Start method with its simple starting instructions:

1. Improves compliance, particularly in adolescents, and
2. Is not associated with an increase in the incidence of breakthrough bleeding or other side effects.

Women who use a 21-day preparation should be cautioned never to exceed the 7 day pill-free interval between packs.

The health-care provider may discuss emergency contraception (EC) as well as providing an EC prescription in advance of need. Dual protection with condoms should be re-emphasized.

A follow-up visit should be scheduled to review the combined OC users' experience, satisfaction, and compliance, as well as to perform a blood pressure check.

If indicated, a pelvic examination can be performed at the follow-up visit.

Progesterone Only Pill (Mini Pill)

It contains low dose a progestin and thus devoid of the side effects of oestrogen in the combined pills. The progestin could be levonorgestrel 75ug, norethisterone 350ug, desogestrel 75ug, lynestrenol 500ug or norgestrel 30ug. The tablet is taken daily from the first day of the cycle. Progestin only pill is started 21 days post-partum, and soon after abortion. The client needs to take precaution in the first 48hrs in the first cycle.

The use of newer generation of synthetic progesterone desogestrel has been encouraging. It has no androgenic effect, no adverse effect on carbohydrate and lipid metabolism, and is considered safe especially for women over 40 years and lactating women.

Mechanism of Action

After taking a mini pill the small amount of progestin in the circulation (about 25% of that in combined pills) will have a significant impact only on those tissues very sensitive to the female sex steroids, oestrogen and progesterone. the contraceptive effect is more dependent on endometrial and cervical mucus effects, because gonadotropins are not consistently suppressed. the endometrium involutes and becomes hostile to implantation, and the cervical mucus becomes thick and impermeable. approximately 40% of patients will ovulate normally[17,18]. tubal physiology may also be affected. the progestin mini pill containing 0.075 mg desogestrel appear to be slightly more effective, probably because it exerts a greater inhibition of ovulation [19]. the change in the cervical mucus requires 2 to 4 hours to take effect, and most importantly the impermeability diminishes 22 hours after administration, and 24 hours some sperm penetration occurs. therefore mini pill must be

taken every day at the same time of the day
.

Contraindications

Mini pills are contraindicated in pregnancy, unexplained vaginal bleeding, recent breast cancer, active liver disease and arterial disease[5].

INJECTABLE

To overcome the inconvenience of daily tablet administration and to improve compliance depot injections were developed. Injectable contraceptives contain hormonal drugs that provide women with safe, highly effective, and reversible contraceptive protection

Two types of injectable contraceptives:

1. Progestogen-only formulations that contain a progestogen hormone and are effective for 2 or 3 months; and,
2. Combined formulations that contain both a progestogen and an estrogen and are effective for 1 month

Progestogen -only Formulations

Consist of DMPA (depot med-roxyprogesterone acetate) and NET-EN (norethisterone enanthate). DMPA is injected every 3 months and NET-EN is injected every 2 months.

Combined Formulations

The most extensively studied formulations are known by their brand names, Mesigyna; Monthly injectable. Mesigyna contains the same progestogen as NET-EN and contains an added estrogen. Administered by a deep intramuscular injection into the muscle of the arm or buttock and are effective immediately. All injectable contraceptives are slowly absorbed into the bloodstream from the injection site, with the body maintaining a sufficient level of hormone to provide contraception for 1 to 3 months, depending on the type of injectable used.

Table 6: Minipill
Advantages & Diadvantages

Advantages

1. Side effects attributed to oestrogen in the combined pill are totally eliminated
2. No adverse effect on lactation and hence can be suitably prescribed in lactating women
3. Easy to take as there is no "on and off" regime
4. It may be prescribed in patients having hypertension, fibroids, diabetes, epilepsy, smoking and history of thromboembolism.
5. Reduces the ris of pid and endometrial cancer.

Disadvantages

1. There may be can, mastalgia, headache, breakthrough bleeding or at times amenorrhoea in 20-30% of cases
2. All the side effects attributed to progestogens may be evident
3. Simple cyst of the ovary may be seen
4. Failure rate is about 0.5-2% per 100 women years of use.

Mechanism of Action

The mechanism of action of progestogen-only injectables (POIS) is different from the other lower dose, progestin only pill because in addition to thickening of the cervical mucus and alteration of the endometrium, the circulating level of the progestin is high enough to effectively block the LH surge, and therefore, ovulation does not occur[20]. FSH is not suppressed as it is with the combination oral pill, therefore follicular growth is maintained sufficiently to produce oestrogen levels comparable to those in

the early phase of menstrual cycle [21].

Efficacy

The reported failure rates of POIs are low, and come within the narrow range of 0.1% to 0.6% [1].

Prevention of Pregnancy

A single injection of POI can provide highly effective protection against pregnancy for two or more months, depending on the formulation. Delivery is simple, independent of coitus, and ensures periodic contact with medical or other trained health personnel.

This is a suitable method for women in whom oestrogens present health risks – e.g., those with a history of thromboembolic disorders - and those who have had side effects with the use of oestrogens.

Non Contraceptive Benefits

Clear benefits

Sickle cell disease: In a two-year trial, women with sickle cell disease using DMPA had significantly fewer crises than women given a placebo [22].

Anaemia: POIs can increase haemoglobin concentration, mainly by reducing menstrual blood loss [1,5].

Possible Benefits

1. Endometrial Cancer:

In a World Health Organization (WHO) study [23], women who had ever used DMPA had one-fifth the risk of developing endometrial malignancy observed in women who had not used DMPA.

The results, although not statistically significant, support the hypothesis that use of DMPA might protect against this form of cancer.

2. Other:

The use of POIs possibly protects against pelvic inflammatory disease (PID), seizures in women with epilepsy, uterine myoma, and endometriosis [24].

COMBINED INJECTABLE CONTRACEPTIVES

Mechanism of Action

Combined injectable contraceptives (CICs) exert their contraceptive effect mainly by suppressing

Table 7: Forms of Injectable Contraceptives

Name	Active Ingredients	Duration of Effect	Common Trade Names
DMPA (progestogen-only)	150mg Medroxyprogestrone acetate in an aqueous microcrystalline suspension	90 days	Depo-Provera, Depo-Clinovir, others
NET-EN (progestogen-only)	200mg norethisterone enanthate in an oily preparation	60 days	Noristerat, Norigest, Doryxas and others
Misegyna (combined)	200mg norethisterone enanthate and 5mg estradiol valerate	30 days	Mesigyna Norigynon

ovulation as in the combined oral pills. In addition, thickening of the cervical mucus (mainly due to the progestagen) presents an obstacle to sperm penetration ascent. The receptivity of endometrium to the blastocyst is also reduced [6].

Efficacy

In clinical trials, Cyclofem /Cycloprovera and Mesigyna/Norigynon have both proved highly effective contraceptives with 12-month failure rates of 0.2% or less for Cyclofem and 0.4% for Mesigyna [1,5,6].

Beneficial Effects

A single injection of a CIC can provide highly effective protection against pregnancy for one month. Delivery is simple and independent of coitus, and in general CICs are associated with better cycle control than POIs.

IMPLANTS

Norplant is sustained release system using tubing permeable to steroid molecules to provide stable circulating levels of synthetic progestins over years of use. The high rate of unintended pregnancies and the relatively high failure rates with the typical use of reversible methods of contraception are strong indications of a need for long acting contraceptive methods that are easier to use. Implantable, subdermal capsules that release progestins for several years are a respond to this need [6]. The long acting progestin methods are as effective as sterilization and intrauterine devices, and MOE effective than oral and barrier contraception [25]. An important reason for this high efficacy in actual use is the nature of delivery system themselves, which require little effort on the part of the user. Because compliance does not require frequent resupply or instruction in use, as with oral contraception, the actual or typical use effectiveness is very close to the theoretical (lowest expected) effectiveness [6].

Sustained release method require less of the user, but they demand more of the clinician. Implants involve minor operative procedures for placement and for discontinuation [6].

Norplant 1.

Norplant was developed by the population council and first approved in 1993 in Finland, where it was manufactured. It was approved in

Table 8: Progestin Only Injections

Advantages

i. The compliance is good.
ii. Easy administration with no worry over missing pills,
iii. The side effects of lipid and carbohydrate metabolism are avoided.
iv. It is suited for lactating women.
v. Avoids oestrogenic side effects.
vi. Many non-contraceptive benefits.

Disadvantages

i. Once administered the side effects need to be tolerated.
ii. Menstrual irregularity and amenorrhoea occurs.
iii. There is delay in return of fertility 6-8 month for DMPA and 3 month for NE-TEN.
iv. The women are clinic dependent.
v. The side effect of weight gain, depression, mastalgia can occur.
vi. It increases LDL but no adverse effect on the blood pressure.

the united states in 1990, marketed in 1991, and withdrawn from the market in 2002 in a business decision dictated by profit and liability despite the fact that it provided an excellent option for contraception [6]. This contains 6 sialistic capsules made of siloxane material of the size 34mmx2.4mm and each containing 36mg levonorgestrel. Its effect last for 5 years [1,5,6].

Norplant 11.

This consist of two rods each containing 70mg levonorgestrel. The daily release of hormone is 50 ug. This was a modification of norplant 1. The two implant system should permit easier insertions and easier and quicker removals and further reduce the visibility of implants in the arm. It provides contraception for 5 years [1].

Implanon

Implanon is a subdermal implant containing etonogestrel, which is a metabolite of desogestrel, a third generation progestagen.

Etonogestrel has poor affinity for androgen receptors and therefore gives fewer androgenic side effects compared to the older second generation progestagens, such as levonorgestrel. It consists of a single closed capsule made of polydimethyl siloxane 40mm x 20mm and contains 68mg of etogestrel which is released about 60 mcg and gradually reduced to 30 mcg per day over 3 years[1,5,6].Implanon is an effective form of contraception, with a Pearl Index of 0.00-0.07 [6], i.e. Pregnancy risk is lower than that seen after tubal occlusion or vasectomy.

The release of the hormone is steady, with slightly higher serum levels seen in the first few weeks. There is a very gradual fall in serum levels over the three years of use [26]. Serum levels are reduced in women who are taking liver enzyme inducing drugs such as rifampicin, griseofulvin, phenytoin and carbimazapine [27]. Serum levels are not affected by concurrent use of oral antibiotics or by gastrointestinal upsets. Serum levels in women over 70 kg are in the lower range; however, the clinical significance of this is uncertain [26].

Steady release of the hormone directly into the blood stream avoids the first pass effect on the liver. Implanon comes in a ready loaded disposable sterile applicator. The needle on the applicator is designed to penetrate the skin readily but is able to tunnel under the skin without puncturing the skin from below. This enables placement of the rod in the superficial subdermal plane, so that the rod is easily palpable.

Mechanism of Action

Etonogestrel inhibits ovulation by the suppression of luteinising hormone release from the pituitary [6]. Serum levels of etonogestrel sufficient to inhibit ovulation are achieved within the first day after insertion of Implanon. Etonogestrel does not completely inhibit follicle stimulating hormone secretion from the pituitary. Some follicular activity is seen in the ovaries, resulting in physiological levels of serum oestradiol. Etonogestrel also produces thickening of the cervical mucus, preventing sperm ascent. Progestagenic changes are also seen in the endometrium, with a decrease in endometrial thickness [28].

The implant can be removed at any time at the woman's request but must be removed at three years. Serum etonogestrel levels become undetectable within a few days after removal of the implant. Studies have shown that pre-existing levels of fertility return rapidly, with 94% of women having ovulated within one month of rod removal[26]. Return to ovulation is

sometimes rapid because of the follicular development seen in the ovary with the etonogestrel implant. Women who do not wish to become pregnant will therefore need to commence another form of contraception immediately after removal of the implant.

VAGINAL AND TRANSDERMAL ESTROGEN- PROGESTIN CONTRACEPTION.

The more option available for contraception, the more effective family planing is within a soiety. vaginal and transdermal oestrogen – progestin contraception have considerable appeal for som women unsatisfied with other methods. an important advantage of vaginal and transdermal steroid contraception is an improvement in coplience achieved by the elmination of a daily regimen of treatment. there ae potential advantages in avoiding the first pass through the liver that is associated with the oral intake of steroids [6].

Vaginal Oestrogen- Progestin Contraception.

The vagina provides an ideal site for contraceptive steroid absorbtion. the stratified squamous epithelium, unlike the skin, is not cornified, permiting easier steroid penetration to the underlying lamina propria, made of colagen and elastin, which is richly vascularised [29]. like subcutaneous, intramuscular, transdermal, and intrauterine contraceptive methods the vagina route avoids gastrointestinal absorbtion and the first pass liver effect.

The Vaginal Ring Method

The nuvaring vaginal steroid contraceptive is a flexible, soft, transparent ring mad of an ethylene vinyl acetate copolymer within silicon bing. The ring is available in only size 4mm in thickness and 54 mm in diameter. the nuvaring releases 15ug ethynyl oestradiol and 120ug etonogestrel per day[30]. Because the progestin and the oestrogen are mixed in the ethylene vinyl acetate core, in the unlikely event of damage to the ring, leakage or higher release of the hormones does not occur. circulating oestrogen and progestin levels reach target concentration within 24 hours. the circulating oestrogen reach a maximun level after 2 to 3 days, etogestrel reaches maximun level after 7 days, and remains stable for 35 days[31]. the ring is inserted by the patient and worn for 3 weeks. The vaginal ring can be initiated in the same fashion as the oral contraceptives, on the first day of menses. routine use requires the insertion of a new ring every 4 weeks to allow for withdrawal bleeding. continous use is obviously an approprite option [32]. Because the ring contains enough steroid hormone to inhibit ovulation for at least 5 weeks [33]. when used continously, a new ring can be inserted every 5 weeks. breakthrough bleeding with the continous use is effectively managed by a 4 day hormone free interval[34].

The ring produces circulating progestin and oestrogen levels that are only 40% and 30% respectively, of the peak levels associated with an oral contracetive containing 150 ug desogestrel and 30 ug ethynyl oestradiol [32]. These levels effectively inhibits ovulation, providing pregnancy rates of less than 1% in clinical trials [30,33]. The mechanism of action is like al combined hormonal contraceptives.

Transdermal oestrogen-progestin contraception.

The transdermal contraceptive patch (ortho-evra) has an area of 20cm^2 (4.5 x 4.5 cm) and three

layers in a matrix type arrangement. the backing outer polymer layer provides support for the middle layer that contains the adhesive and the hormones, and the inner layer is a polyester liner that is removed from the adhesive layer just before application. The size is that required to deliver an effective dose of steroid hormones. the pach contains 750 ug ethynyl oestradiol and 6 mg of norelgestromin and delivers 20 ug ethynyl oestradiol and 150 ug norelgestromin each day when applied to discrete locations on the lower abdomen, upper outer arm, the buttock, or the upper torso (excluding the breast). norelgeromin still undergoes liver metabolism with transdermal application; however, the resulting metabolite, levonorgestrel, is highly bound to sex hormone binding globulin, limiting its biologic impact. about 97% of norelgestromin is bound to albumin and 3% is unbound [35].

The patch is applied on the same day, but not on the same site, once each week for 3 weeks, followed by a week without use of the patch. as with oral contraceptives, patients and clinicians may choose to use the contraceptive patch continously, eliminating withdrawal bleeding.
transdermal contraception produces the same spectrum of actions with oral contraceptives, achieving the same high level of efficacy[6]. therefore, the same considerations reviewed in this chapter on oral contraception apply to transdermal contraception (as well as the vaginal ring), including the same contraindications and non contraceptive benefits.

EMERENCY CONTRACEPTION

Emergency contraception (EC) is any method of contraception which is used after intercourse and before the potential time of implantation as these methods work prior to implantation, they are not abortifacients. Emergency contraception is a backup method for occasional use, and should not be used as a regular method of birth control.

There are 2 methods of emergency contraception:

1. Hormonal methods, which involve the use of emergency contraceptive pills (ECPs), and
2. The post-coital insertion of a copper intrauterine device (IUD).

Two hormonal preparations are :

1. One contains only the progestin levonorgestrel, while the other is a
2. Combined preparation containing both ethinyl estradiol and levonorgestrel.

The levonorgestrel-only method, (The regimen consists of 2 doses of 750 µg levonorgestrel taken orally 12 hours apart) [36]. A single dose of 1.5 mg of levonorgestrel appears to be as effective as the standard 2-dose levonorgestrel regimen [37].

Yuzpe method in use since the 1970s, it consists of the oral administration of 2 doses of 100 µg ethinyl estradiol (EE) and 500 µg levonorgestrel 12 hours apart [38]. Ovral tablets (each containing 50 µg ethinyl estradiol and 250 µg levonorgestrel) are most commonly used to provide these doses. The Yuzpe and levonorgestrel-only methods have been shown in randomized trials to reduce the risk of pregnancy by approximately 75 and 85% respectively [37]. Although they have generally been used only up to 72 hours after intercourse, both hormonal methods of EC are effective when taken between 72 and 120 hours after unprotected intercourse[39]. The effectiveness when used after 72 hours seems to be slightly lower. Effectiveness decline significantly with increasing delay between unprotected Intercourse and

the initiation of treatment.

Copper IUD: the introduction of a copper IUD within a maximum period of 5 days can prevent conception following accidental unprotected exposure. This prevents implantation. Failure rate is about 0.1 per cent [40].

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