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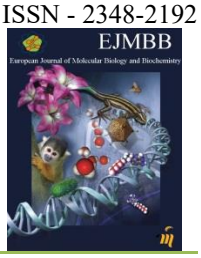

HORMONAL CONTRACEPTIVES: PHARMACOKINETICS, SAFETY, AND INNOVATIONS

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ABSTRACT

Since the 1960s when the hormonal contraceptives were introduced, they have developed and have provided a wide range of options to suit the varied reproductive health requirements. These forms of contraception that exist in the form of oral pills, patches, implants, and injectables, act mainly by preventing ovulation, modifying the cervical mucus, and transforming the endometrial lining in order to prevent pregnancy. Solutions are also increased by the creation of non-oral delivery systems and new technologies, including long-acting reversible contraceptives (LARCs) and male contraceptives. There are, however, side effects and risks associated with their use such as weight gain, thromboembolism, and cancer, and medical history and lifestyle factors should be taken into consideration carefully. There has never been a bigger need of such individualized methods of contraception due to individual health status, cultural beliefs and access disparity. Contraceptive equity, informed consent, and respect of autonomy are the keys to the fact that every person may make informed and voluntary decisions concerning their reproductive health.

INTRODUCTION

Worldwide Situation of Birth Control

The use of contraceptives is a family planning and reproductive health factor that is of critical importance throughout the globe, and they give people the option of managing their fertility and take well-informed choices on how and when they wish to have children. Contraceptive use is affected by a number of social, cultural, economic, and political factors in the global context. [1, 2] In most regions across the world, access to contraceptives methods is highly linked to issues of gender equality, health education and community health facilities. Although the use of contraceptives has improved tremendously over time, in some areas especially in the low-income nations, the use of modern contraceptives remains low owing to the social stigma, mis-information and poor medical systems. Nevertheless, the adoption of contraception in the world has resulted in a significant effect on the maternal and child health, the empowerment of women, and allowing couples to plan their families in a way that is more reflective of their personal and fiscal situations. [3–5].

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Hormonal contraceptives are also being developed.

Hormonal contraceptives have experienced a great evolution since its beginning when the choices were limited in form and varieties, it has come to offer a variety of choices that can meet a wide range of needs and preferences. The introduction of the first oral contraceptive in the 1960s changed the birth control process as it was an easy and effective way of preventing pregnancy among women. Hormonal contraceptives have since undergone some development due to the progress in medical research that led to the development of numerous formulations such as oral pills, patches, implants and injectables. The recipes are now more sophisticated with less amount of hormones to minimize side effects without compromising on effectiveness. Also, non-oral delivery systems have been invented using innovations like intrauterine systems and subdermal implants, which are more long-term. The emphasis on enhancing safety, convenience and

acceptability of the hormonal contraceptives has remained a dominant factor in the reproductive health arena broadening the choices of people all over the world.[6,7]

Demand of Innovation and Unique Choices.

The necessity of innovation of contraceptive practices has never been as high since people want more individualized and more accessible ones that can suit the particular lifestyle and health requirements. [8,9]The existing range of contraceptives, even though efficient, might not be applicable to all people because of differences in medical conditions, side effects as well as personal preferences. As an example, one might have a negative reaction to certain hormones and another one may favor the one that involves fewer visits to a medical care provider or ones that are durable. Moreover, the new avenues of study point to the necessity to customize contraceptive practices to satisfy the special needs of the individuals, such as the age, weight, medical history, and lifestyle decisions. Efforts at more hormonal contraceptives are also aimed at reducing side effect, enhancing non-oral administration, and seeking more sustainable and long-lasting methods. With the world population becoming more and more diversified, there is the growing need of contraceptive methods which are flexible, convenient and above all individualized so that everyone may find the means that suits him or her best in terms of health and life conditions.[10–12].

Classification of Hormonal Contraceptives

Combined hormonal contraceptives (CHCs).

Combined Hormonal Contraceptives (CHCs) represent a widely used birth control method which includes two hormone types an estrogen and a progestin. These contraceptives are effective in preventing ovulation, thickening of the cervical mucus to block entry of sperm and also in changing the uterine lining to block implantation. CHCs can be designed as per the preference and needs of users and are therefore available in different forms.[13–15]

Combined Oral Contraceptives Pills (COCPs).

The most common type of CHCs are the Combined Oral Contraceptive Pill (COCP). It has artificial forms of the hormones estrogen (ethinylestradiol) and progestin. The COCP is usually administered on a daily basis and it prevents ovulation as well as alters the cervical mucus such that the sperm finds it hard to access the egg. COCPs, though quite effective under the right circumstances, demand that the dosage should be observed on a regular basis. They also have a number of non-contraceptive health benefits, including controlling menstrual periods, acne and cancer of some types. Nevertheless, they can also cause side effects including nausea, weight gain and greater risk of developing blood clots particularly among women who smoke and over 35 years.[16,17]

Transdermal Patches

The contraceptive patch is a transdermal contraception that is a combination of hormonal contraception. It emits the same hormones (estrogen and progestin) as the COCPs but ones that are released through the skin. This patch is placed on the skin (usually on the lower abdomen, buttocks or upper arm) and is used once a week. The patch is changed every three weeks during the first 3 weeks and the fourth week is allowed as a withdrawal bleed resembling a menstruation. [11,18]The patch offers a more convenient, covert means of providing women with a more convenient way of taking daily pills, since they might forget to do so. Nevertheless, it should be used with only a little caution by its users and the patients with some health problems might be reluctant to use it because of the likelihood of side effects of the hormones like blood clots.[11,16,19]

Vaginal Rings

Another type of combined hormonal contraception is the vaginal ring. This is a flexible ring and is usually around 2 inches in diameter, which is placed inside the vagina, where it discharges estrogen and progestin directly into the bloodstream. Three weeks are spent wearing the ring, and one week without it in between so that there can be a withdrawal bleed. The pill is equally effective as the ring and can be taken by the women who do not want to take medication on a daily basis. It has the benefit of a more stable release of hormones and eliminates the fluctuations that may be experienced with daily pills. The patch is associated with certain risks, and so does the ring (blood clots, vaginal irritation, discomfort, etc.).[17,20,21]

Progestin-Only Contraceptives

Progesteron-only contraceptives are contraceptives that, as the name implies, are only made up of a synthetic variety of progesterone (progestin) and do not include any estrogen. They are also good to those people who are unable to sustain estrogen because of a medical condition like having had blood clots, breastfeeding mothers, or females who have side effects of estrogen. Progestin-only birth control is mainly used to make the cervical mucus thick and the uterine lining thin, thus resulting in the immobility of the sperm to penetrate the egg and fertilize it.[16,22]

Mini-Pills

The mini-pill is called the progestin-only pill and has a reduced amount of progestin than other hormonal contraceptives. It is administered on a daily basis and there is no interruption and must be administered at same time daily to ensure its effectiveness. Mini-pill has been known to be of choice by breastfeeding mothers or women who are unable to take estrogen. Though it is an effective method of preventing pregnancy, its use is sometimes associated with irregular bleeding, spotting or alteration of

menstrual cycles. Nonetheless, it is a perfect choice among women requiring a low dosage hormone preparation or those who have certain health-related issues with estrogen.[23,24]

Depot Injections (e.g., DMPA)

Depot Medroxyprogesterone Acetate (DMPA) is a progestin-only injectable birth control which delivers long-term birth control. DMPA is used in the form of an intramuscular injection at intervals of 3 months and acts by preventing ovulation and thickening of cervical mucus. It is one of the best contraceptive means with less than 1 percent failure rate when used at the right time. It is especially effective among women that do not want to take a daily pill. Nonetheless, weight gain, bone loss, and abnormal menstrual bleeding have been mentioned as the possible side effects. Bone health should be monitored among long-term users, particularly those who have been using the method during more than two years.[23,25]

Implants and Hormonal IUDs

Long-acting reversible contraceptives (LARCs) are implants and hormonal intrauterine devices (IUDs), which offer pregnancy prevention with a high level of effectiveness. The hormonal implant is a small and flexible rod which is placed under the skin of the upper arm and emits a constant dose of progestin over a span of 3-5 years. The hormonal IUD is a device that when inserted into the uterus, releases progestin into the surrounding, which stops pregnancy that can last up to 3-7 years, depending on the kind.[26] The advantage of both approaches is that they provide long-term contraception with a low user dependency. They are very effective with less than 1 per cent. failure rates. Nevertheless, other women can get side effects, including abnormal bleeding, mood swings, or even pain around the IUD. They both are appropriate in women who desire a set-and-forget form of contraception and also they are the best in the case of a woman who would like to have long term pregnancy prevention without the need to be addressed on a daily basis.[27]

Pharmacokinetics of Hormonal Contraceptives

Absorption and Bioavailability.

The bioavailability and absorption of hormonal contraceptives are the most important factors to be considered in their effectiveness. Bioavailability is the percentage of dose given which is absorbed into the systemic circulation in its active form. The route of administration is a major factor in determining the absorption of a drug as well as the speed at which it works. Different routes of absorption of hormonal contraceptives are possible, and each route has its considerations in the bioavailability.

Oral vs. Non-Oral Routes

Hormonal contraception mostly occurs through oral forms of contraception which are ingested through the gastrointestinal tract. Oral contraceptives determine their bioavailability based on their absorption in the stomach and the small intestine. Nonetheless, oral contraceptives are first-passed in the liver, and this may decrease their bioavailability. Non-oral methods, e.g., transdermal patches, vaginal rings, implants, by-pass the gastrointestinal tract and the liver to some extent, which leads to increased bioavailability and consistency of hormones in the bloodstream. The alternative routes may also have the advantage of minimizing the occurrence of gastrointestinal side effects and enhance adherence since the alternative routes are administered less often than oral pills that are taken daily.[20,28]

The Metabolism of the first-pass in the liver.

First-pass metabolism can be defined as a metabolism occurring in the liver prior to the drug entering the systemic circulation. In the case of oral contraceptives, there is absorption of the hormones into the blood by the gastrointestinal tract which is then transported to the liver where it is metabolized partially before going into the systemic circulation. The process depletes the levels of active drug in the bloodstream, which has an overall impact on its effectiveness. The degree of first-pass metabolism may differ in accordance with the type of hormone and formulation, and the degree of first-pass metabolism is also a crucial element when calculating the dose of the oral contraceptive.[29]

Distribution and Plasma Protein Binding.

Hormonal contraceptives once absorbed are distributed throughout the body with a large proportion of the drug bound to plasma proteins. Hormone binding to proteins like albumin and sex hormone-binding globulin (SHBG) is important in the regulation of their availability and activity.

Sex Hormone Binding Globulin (SHBG)

Sex hormone-binding globulin (SHBG) is a plasma protein, which binds sex hormones e.g. estrogen and testosterone. Combination of estrogen and progestin with SHBG influences their active free form in the body. In a scenario of high SHBG levels, the proportion of the hormones bound is higher and thus the concentration of free hormone to bind to its receptor, and hence its action may be lower. Hormonal contraceptives may alter SHBG levels, the estrogen-containing methods tend to elevate the SHBG levels which may affect the pharmacodynamics of the drug and affect its performance.[30]

Favoritism in volume of distribution.

The volume of distribution (Vd) is used to determine how much a drug is dispersed in the body tissues compared to the plasma. The Vd of hormonal contraceptive may vary depending on the formulation and route of administration. Oral contraceptives can indeed be a better choice because, when compared to transdermal

patches, they might have a higher Vd, with initial liver metabolism consumed and less tissue distribution of the hormones. Vd may interfere with the action time and the time needed by the drug to reach its steady-state in the bloodstream. The variation in side effects and efficacy of hormonal contraceptives of different types may also be a result of difference in Vd.[31,32]

Metabolism

Hormonal contraceptives are metabolized mainly in the liver whose enzymes change the drugs to be eliminated out. Genetic factors, drug interactions and other personal health factors affect the metabolic processes. It has been found that enzymes involved in the metabolism of these drugs can differ in their activity, and they can alter the effectiveness and safety profile of contraceptive mechanisms.

Enzymes Involved (Hepatic CYP Enzymes) CYP3A4

The P450 enzymes especially CYP3A4 are major in metabolisation of most hormonal contraceptives. The oxidative metabolism of most drugs such as oral contraceptives is caused by CYP3A4. This enzyme is concerned with the breakdown of the hormones in the liver, changing its structure in order to be excreted by the body more easily. The metabolism of hormonal contraceptives may be influenced by variations in the activity of CYP3A4 caused by genetic differences or drug interactions and have an effect on the effectiveness of hormonal contraceptives. To illustrate, some drugs which initiate the CYP3A4 activity like anticonvulsant may speed up degradation of contraceptive hormones, and thus may lower their efficacy.[32–34]

Drug-Drug Interactions

The interaction of drugs with drugs is also a big factor in the use of hormonal contraceptives. Drugs that can change the activity of liver enzymes like CYP3A4 may change the contraceptive hormone metabolism and cause either low efficacy or higher risk of side effects. As an example, the activity of CYP3A4 can be provoked by drugs such as rifampin or carbamazepine, and this could cause a reduction in the concentration of contraceptive hormones and an increased risk of contraceptive failure. On the other hand, drugs that block CYP3A4 may raise hormone levels, which may cause such side effects as breakthrough bleeding or cause thromboembolic events at risk.

Elimination and Half-life

Elimination is the process of the body excretion of a drug, which excretion is mainly by the kidneys or liver. The half life of a drug is the duration taken by the concentration of a drug in the bloodstream to reduce by half. Of significance in defining dosing schedules and duration of action of hormonal contraceptives are the half-life.

The Comparisons of Estrogen and Progestins.

The pharmacokinetic characteristics of estrogen and progestins vary, such as half-lives of their elimination. Estrogen possesses a rather low half-life, which prompts the need to be taken regularly in oral contraceptives preparations.[17,35] On the other hand, progestins are expected to have longer half-lives, which allows a lower frequency of dosing in the forms of injections, implants, and IUDs. The variability in half-life of estrogen and progestin formulations could affect the overall pharmacokinetic profile of the combined hormonal contraceptives and could affect the side effects, effectivity and user preference of various contraceptive methods.

Missed Doses Implication and Compliance Implication

Hormonal contraceptives have a half-life which has a significant impact on patient adherence and missed doses. In the case of contraceptives, which may have a short half-life, such as COCPs, one missed dose may considerably impair its effectiveness in preventing pregnancy, because the amount of the drug in the body may become low enough to be below the therapeutic threshold. By comparison, longer half-life regimens, including implants or depot injections, provide a greater safety of dose tolerance: because sustained-release preparations have a therapeutic concentration longer, there is a larger safety margin due to missed doses. This is because patient adherence to dosing schedules is very important in ensuring that hormonal contraceptives remain effective and those with longer half-lives could serve to enhance adherence to the contraceptive particularly among women who find it difficult to take pills daily.[19,20]

Mechanism of Action

Inhibition of Ovulation

Ovulation inhibition is one of the major effects of hormonal contraceptives. The ovulation is the release of a mature egg in the ovary and inhibition of the ovulation is vital in the prevention of pregnancy. Hormonal contraceptives do this by changing hormonal environment in the body especially by modulating gonadotropin-releasing hormone (GnRH) and inhibiting follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Such changes inhibit the ovulation and development of an egg and no ovulation during a menstrual cycle occurs.[36,37]

Dampening of LH and FSH Secretion.

Major hormones in the regulation of the female reproductive system are LH and FSH. LH causes ovulation, and FSH affects the growth and development of follicles in the ovaries. Hormonal birth control, particularly estrogen and progestin-containing, contraceptives, do not prevent the release of estrogen and progestin hormones by the anterior pituitary gland. This suppression inhibits the growth of ovarian follicles and the resultant release of an

egg and hence fertilization. Contraceptives contain estrogen that inhibits the release of FSH whereas progestin inhibits the increase of LH that causes ovulation. This bilateral inhibition is also effective to botch the ovulation, which will not allow the pregnancy.

Feedback Inhibition at Hypothalamus-Pituitary Axis.

The hypothalamus-pituitary axis is considered to be a key in the management of the menstrual cycle through the regulation of secretion of gonadotropins, LH, and FSH. At this axis, hormonal contraceptives act by feedback inhibition. Contraceptives disrupt the regulation of the hypothalamus and pituitary by introducing synthetic estrogen and progestin in the system that would normally control the feedback signals used in regulating the hypothalamus and pituitary. [38,39]These hormones are a cue to the hypothalamus and pituitary stimulating the production of GnRH which consequently inhibits the release of FSH and LH. This causes a disruption of the whole cascade, which results in ovulation. This feedback system plays a vital role in the prevention of ovulation and, hence, pregnancy.[40,41]

Cervical Mucus and Endometrial Lining changed.

Along with stopping ovulation, hormonal contraceptives have the effect of modifying the cervical mucus and the endometrial lining. These alterations complicate the reaching of the egg by sperm and block implantation of a fertilized egg to the uterus resulting in an increased contraceptive effect. These mechanisms are used together with ovulation suppression in order to give a complex intervention to prevent pregnancy.

Impaired Sperm Penetration

Hormonal contraceptives change the regularity and characteristics of cervical mucus that is made thicker and more viscous. In most cases, cervical mucus varies in consistency during the menstrual cycle thickening during ovulation to allow the movement of sperm through the cervix. Nevertheless, the hormonal contraceptives induce the mucus to be thick and non-porous forming a barrier that prevents the movement of sperm. This change in the cervical mucus greatly decreases the possibility of the sperm penetrating the egg, even in case ovulation took place. The mucus is also thickened and acts as an extra protective mechanism against pregnancy.[42,43]

Prevention of Implantation

The contraceptives in the form of hormones also cause changes in the endometrial lining of the uterus rendering it less hospitable to a fertilized egg. In the normal menstrual cycle, the endometrium becomes thickened in order to allow the possible implantation of a fertilized egg. But in hormonal contraceptives, the hormonal milieu does not allow the endometrium to be developed in the situations required in the implantation process. [44–46]Consequently, fertilization will not be followed by successful implantation of the fertilized egg in the uterus resulting in non-pregnancy. This action is especially significant in such practices as progestin-only pills, implants and IUDs, the main mechanism of which is this.

Clinical Efficacy and Usage Patterns

Efficacy Metrics

The effectiveness of the contraceptive techniques is an essential value in defining its effectiveness in preventing conception. It is often measured by the failure rates of various contraceptive methods, under perfect use conditions (perfect use) and under real use conditions. [11,47]The knowledge of these metrics can be used to measure the effectiveness of contraception as a whole and the extent of dependence on the user behavior.

Typical vs. Perfect Use

Efficacy measures are commonly classified as normal use and ideal use rates. Perfect use is whereby a contraceptive method is used as prescribed and no errors are made. On the contrary, typical use considers the use of the method in the real-world context where errors or failures in following the method can be experienced. Perfect use rates are the best case situation and usually under perfect use, there is less contraceptive failure. Nevertheless, failure rates in the real-world are more likely to be higher because of erratic use or missed doses or incorrect application. As an example, with perfect usage, oral contraceptives have an extremely low failure rate, but with normal usage an extremely high failure rate, mainly because of missed pills. Thus, it is necessary to know both application situations to advise patients about the predicted effectiveness of the method they have selected.[47]

Failure Rates by various Populations.

The success of contraceptives among different populations may differ because of the various factors involved such as age, health, socioeconomic and education. The failure rates of some techniques among younger people (teenagers, in particular) might be greater because of the non-use of the techniques or improper training. Besides, women who have some health conditions including obesity and metabolic disorders might have lower efficacy rates with some forms of contraceptives. An example is that the use of oral contraceptives can be ineffective in persons with an increased body mass index (BMI). On the same note, cultural influence, access to health and even education can also impact the efficiency of the contraceptive use and this can in turn influence the rates at which failures occur. Thus, it is very important to take all these factors into consideration when prescribing contraceptives to make sure that the chosen means is the most effective one in the definite case.[48,49]

Issues of Adherence and Compliance.

Contraceptive use must be followed by taking contraceptives to make their use effective. The failure to adhere to the prescribed usage pattern may greatly affect the effectiveness of contraceptive techniques. Issues that affect adherence are frequency of administration, ease of administration, adverse effects and patient education and support.

Daily vs. Long-acting Methods

Daily regimens are more difficult to adhere to like oral contraceptives because the user has to remember to take the pill every day and at the same time. Lost doses may cause a major loss in efficacy, which will cause unwanted pregnancies. Conversely, long acting reversible contraceptives (LARC) like implants, intrauterine devices (IUDs), and depot injections have a higher adherence because the intervention is not as frequent. These solutions have a set-and-forget quality, with hormonal implants and IUDs lasting several years and depot injections only having to be given after every three months. Consequently, LARCs are more effective and show less failure rates because of the enhanced compliance. LARCs can be the most appropriate choice of women who have problems remembering medications each day or who want the long-term solution.[11]

Purpose of Counseling and follow-Up.

Routine follow-up and counseling is a key to enhance adherence and compliance to contraceptive methods. Through counseling, the patients are given very valuable information on how their adopted approach operates, what side effects would occur, and their usage. It can also enable healthcare providers to discuss any issues of concern or misperception that can influence adherence[11,50]. The follow-up visits are also very valuable as they will give the chance to check the efficiency of the method used, discuss any difficulties, and remind the patient of the need to follow the method. Periodic monitoring can be used to reveal and correct problems with the use of methods, including the inability to remember taking daily doses or control side effects. Through continuous encouragement and education, patients may be encouraged to stick to their contraceptive plan and thus, minimize the possibility of contraceptive failure[11,51].

Safety Profile and Side Effects.

Common Adverse Effects

Although hormonal contraceptives are considered very effective in preventing pregnancy, they have a list of side effects. Such side effects differ with an individual and the kind of contraceptive one takes. The majority of side effects are not severe but fade away with the course of time, yet there are those that may not go away and in fact affect the quality of life of an individual. Patients should not be afraid to talk to their health providers about the possible side effects in order to select the most appropriate approach.

Gaining of weight, Nausea, Breast Tenderness.

The most widely reported effects of hormonal contraceptives include weight gain, nausea, and breast tenderness. The increase of weight can be caused by the alteration in the appetite, fluid retention, or metabolic impact of the hormones. Even though the evidence of the hormonal contraceptives creating a dramatic weight gain is inconclusive, some women have reported to have gained weight at a modest rate. Another side effect is nausea, especially when oral contraceptives are taken, but sometimes it goes away in the initial few months.[13,52] The symptoms of breast tenderness also appear very often and can be quite uncomfortable particularly during the first phases of taking hormonal contraceptives. These symptoms are usually short-term, although they can be irritating and the patients need to tell their health providers when they become so serious or chronic.[10,53]

Menstrual Irregularities

Normal menstrual cycle may be derailed by hormonal birth control and in particular estrogen and progestin containing birth control. Contraceptives have been observed to alter most women in terms of their frequency, duration and flow of their periods. Some of these changes may be light or heavy bleeding, spotting between periods or even no menstruation whatsoever, seen to be common with long-acting contraceptives such as implants or injectable formulations. Whereas a few women might be pleased by these alterations (lighter or no period), some women can have irregularized bleeding, and this can be frustrating. Menstrual irregularities usually resolve after the initial few months of the usage but in certain cases, it may continue to persist and one may need to alter his or her contraceptive method.[11,54]

Serious Risks

Although hormonal contraceptives are usually safe, they risk being severe to some groups of people. These risks should be known and compared to the advantages of contraception especially in women who have underlying health conditions or who are prone to more complications.

Thromboembolism and Cardiovascular Events.

One of the most dangerous risks of using hormonal contraceptives is known as thromboembolism; it is the development of blood clots that may be transported to the lungs, brain, or heart. Combined oral contraceptive pills, patches, and vaginal rings contain estrogen, which is a contraceptive that increases the risk of venous thromboembolism (VTE), which may result in deep vein thrombosis (DVT) or pulmonary embolism (PE). The women who smoke and are above the age of 35 and those who have a history of blood clots are at a higher risk.

Besides thromboembolism, hormonal contraceptives may lead to cardiovascular events i.e. heart attack or stroke especially in women with risk factors such as high blood pressure, overweight or women with a history of a cardiovascular disease. This is the reason why women who are highly susceptible to cardiovascular events should not be encouraged to use estrogen-impregnated contraceptives.[17,55]

Risks of Cancer: Breast, Cervical, Ovarian.

Research is being done to determine the association between hormonal contraceptives use and cancer risks. Research has revealed that hormonal contraceptives have a minor probability of raising the risk of some types of cancers and protecting against others.

- Breast cancer: Cases show that the risk of breast cancer is somewhat augmented in women who utilize hormonal contraceptives, especially those who use them over a long duration or those who begin it at a young age. The risk however becomes normal upon stopping the contraceptive.
- Cervical cancer: It has been estimated that hormonal contraceptives, when used long-term, tend to increase the risk of cervical cancer, particularly in women who have more than one sexual partner or are infected with human papillomavirus (HPV).
- Ovarian cancer: Conversely, hormonal contraceptives have been found to lower the ovarian cancers. This protective action builds up with the number of years of usage and may continue to be observed long after withdrawal.
- On the whole, the cancer risks of hormonal contraceptives are usually minor and the contraceptive advantages vastly exceed the dangers of the same with the majority of women. The personal risk factors however must be taken into consideration when deciding a contraceptive method.

WHO Medical Eligibility Criteria.

The World Health Organization (WHO) offers medical eligibility requirements on the usage of contraceptives where women are divided into various risk groups based on the state of their health. The standards assist medical staff to make sound judgments regarding the use of safe contraceptive procedures to individual patients. Women who have some conditions, including a history of blood clots, uncontrolled hypertension, liver disease or some forms of cancer are perhaps advised not to use hormonal contraceptives. [56,57]An example is that women who are in history of stroke or myocardial infarction are not supposed to take contraceptives that contain estrogens, whereas those with diabetes or obesity might have to be monitored more closely when using the methods. The guidelines provided by WHO give much importance to risk assessment at an individual level and prescribe the use of alternative measures where appropriate.[58, 59]

Table 1: Classification of Hormonal Contraceptives.

Contraceptive Type	Method	Hormones	Administration	Key Benefits	Possible Side Effects
Combined Hormonal Contraceptives	Combined Oral Contraceptive Pills (COCPs)	Estrogen	Oral, daily	Controls periods, acne, reduces certain cancers	Weight gain, nausea, blood clots
Transdermal Patch	Estrogen	Transdermal, weekly	Convenient, less frequent dosing	Skin irritation, blood clots	
Vaginal Ring	Estrogen	Vaginal, 3 weeks on, 1 week off	Stable hormone release, no daily pills	Vaginal irritation, blood clots	
Progestin-Only Contraceptives	Mini-Pill	Progestin	Oral, daily	Suitable for breastfeeding, no	Irregular bleeding, spotting
Depot Injections (DMPA)	Progestin	Injection, every 3 months	Long-term, low failure rate	Weight gain, bone loss,	
Implants & Hormonal IUDs	Progestin	Subdermal or uterine, long-term	High effectiveness, low user dependency	Mood swings, irregular bleeding	

Table 2: Common Side Effects of Hormonal Contraceptives

Side Effect	Description	Contraceptive Methods Affected
Weight Gain	Increase in body weight due to fluid retention or metabolic effects.	COCPs, Depo-Provera, Implants
Nausea	A feeling of nausea, particularly during the first few months.	COCPs, Patches
Breast Tenderness	Discomfort or swelling of the breasts.	COCPs, Patches, Rings
Irregular Bleeding	Spotting or changes in menstrual cycle length or flow.	Mini-Pills, IUDs, Depo-Provera
Mood Swings	Emotional changes or fluctuations in mood.	Patches, Rings, Implants
Thromboembolism	Blood clots leading to severe complications like DVT or PE.	COCPs, Patches, Rings

Table 3: Special Considerations and Risk Stratification for Hormonal Contraceptive Use

Risk Factor	Recommended Contraceptive Methods	Considerations
Age >35 & Smoking	Progestin-only methods, LARCs	Increased risk of cardiovascular issues
Obesity (BMI >30)	Implants, IUDs	Oral contraceptives may be less effective
History of Thromboembolism	Progestin-only methods, LARCs	Avoid
History of Cancer (e.g., breast)	Progestin-only methods, LARCs	Estrogen
Epilepsy or Antiepileptic Use	Higher doses of hormonal contraceptives or LARCs	AEDs reduce contraceptive effectiveness
Lactating Women	Progestin-only methods (Mini-Pill, IUDs)	Estrogen

Figure 1: Drug Interactions and Special Populations

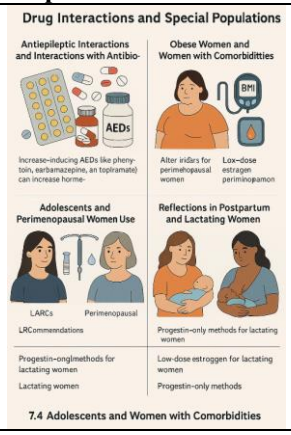

Figure 2: Innovations in Hormonal Contraception

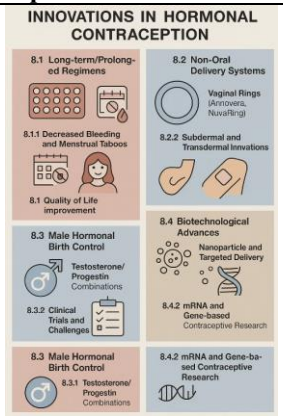

Figure 3: Ethical, Social, and Access Considerations

CONCLUSION

Hormonal birth controls have had a significant effect on the reproductive health that gives women a certain power to regulate their fertility and organize their families based on their own, economical and health conditions. Since the launch of the first oral birth control in 1960s and the advent of novel, non-oral technologies like implants, patches and IUDs, the history of hormonal contraceptives is made up of significantly increased options. The combination of these developments with an increased awareness of pharmacokinetics and the creation of more personalised choices has improved the safety, efficacy, and accessibility of contraception all over the world. Nevertheless, hormone-based contraceptives provide a good and effective method of pregnancy prevention however, they have their difficulties. The threat of side effects like weight gain, thromboembolism, and the possibilities of a long-term impact on health precondition the careful selection in regards to the needs of a patient, their medical history, and lifestyle. Besides, the equilibrium of equity, access, and cultural factors have still been dominating the usage of contraceptives in various locations and among various groups of people and it is therefore important to have continuous work in health education, informed consent, and enhancement of reproductive autonomy. Innovations such as male contraceptives, nanotechnology and gene-based technique (among others) are the future of contraception which could provide even more personalized, efficient and affordable solutions. Conclusively, provision of contraceptives that are safe and effective to people irrespective of their upbringing is a key component to gender equality, bettering of population health, and enabling people to make knowledgeable choices concerning their reproductive destinies.

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