

Combined Hormonal Contraceptives – An Update



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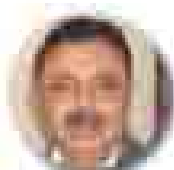
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PRESIDENT'S MESSAGE



*Let's make a new Indian woman
Literate and healthier*

FOGSIANS only you can make a difference

This second FOGSI FOCUS on hormonal contraception comes to you edited and compiled by Dr. Sachitra Pandit and Dr. Mandarini Pathak.

Contraception awareness is the need of the day. Our country is on the brink of an economic and developmental explosion and along with this we are also facing the population explosion.

Why are we not able to stabilize our growing population and why are we not able to offer effective contraceptive services to our women? There are two reasons the major being social awareness and acceptability and the minor being that the service provider has to be convinced and educated about the newer advanced methods available.

FOGSI FOCUS is aimed to educate and to update the FOGSIANS about important and relevant issues.

This FOGSI FOCUS on hormonal contraception addresses all the issues, myths, misconceptions and prescribing information.

All contributing authors have done a wonderful job and the editors have made the manuscript a fantastic document.

I hope you all will read this, absorb and use the knowledge.

Happy reading!

Remember our motto...

Educate, Prevent & Empower

Only you can make a difference.

With Warm Regards,

Dr. Narendra C. Malhotra
President - FOGSI

FOGSI thanks **Cipla** for supporting this issue.

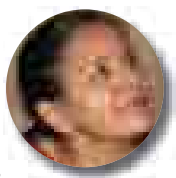


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EDITORIAL

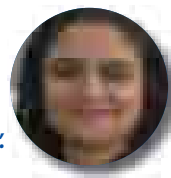


This year the FOGSI theme focuses on making the **'Indian women literate and healthier'**. In keeping with this theme as **Vice President of FOGSI** we have launched **FOGSI Ankur initiative** which aims at – educating the underprivileged women and their family members about the importance of antenatal care. By involving them in their own health care we are encouraging them to register early in the nearby hospitals for delivery; prevent anemia by dietary changes and daily intake of iron tablets; and do financial planning.

Our FOGSI **President, Dr. Narendra Malhotra** has also entrusted me with the job of conducting workshops for **'Updates in Caesarean Skills'** to help our colleagues so that a better quality of care can be offered to the pregnant women undergoing a caesarean section. We have an excellent compilation of video presentations from various expert FOGSIANS, for this purpose and the response has been overwhelming!!

One issue that concerns all of us is to educate people on the importance of contraception and acceptance of a small family. That is why we have focused on Contraception update in our FOGSI FOCUS. Dr Mandakini Parihar has done a superb job as the Chairperson of the Family Welfare committee of FOGSI and has contributed immensely to this issue of FOGSI FOCUS. I am sure that not only does it make good reading but is also of immense utility to all of you to counsel your patients in a better manner.

Dr. Suchitra Pandit
Vice President, FOGSI
Professor and Unit chief,
LTMGH, Sion, Mumbai



"Nothing in this century, not even the right to vote, made such an impact on women's lives as the advent of The Pill".

Ladies Journal, 1990.

48 Years of the Pill – the advent of hormonal contraceptives.

On May 9, 1960, the FDA approved the sale of the first hormonal contraceptive for use – The Pill. Margaret Sanger died in September 1966 with a dream fulfilled of an effective, safe, female-controlled contraceptive pill...Her *"Magic Pill"*.

The Pill has evolved with many additional benefits along with research in developing other forms of hormonal contraceptives and newer delivery systems for hormonal contraceptives. All modern hormonal contraceptives have used the Pill as their bench mark in achieving successful prevention of pregnancy.

All that the little hormone tablet does is to temporarily prevent pregnancy, yet the transformation of women's lives since the pill was introduced has been nothing short of breathtaking. Today, women can get a prescription for a Pill containing newer progesterone and using anti-androgenic progesterone has made the Pill **safer and more friendly and hence more compliant.**

In this issue of FOGSI FOCUS on "Combined Hormonal Contraceptives" we have highlighted all the different types of options available for hormonal contraception. There is a detailed discussion on all its beneficial side-effects and the harmful effects and the WHO eligibility criteria for the use of hormonal contraceptives. The common myths surrounding the PILL have been discussed along with current issues like the scare of cancer, thrombosis and HIV. Practical solutions to common clinical situations like the missed pill, when to start the pill, who should not be given the pill etc. have been explained for better understanding. This **education** will help create positive awareness and help our patients make their informed choices and help us **prevent** unwanted pregnancies and **eradicate** population explosion.

I thank our President Dr. Narendra Malhotra for inviting me to be the editor for this very important issue on "Combined Hormonal Contraceptives". I must thank all the contributors for their excellently researched chapters and their timely submission, my co-editor, Dr. Suchitra Pandit for her help and inputs, Cipla and their team for seeing that this issue is ready on time. Last but not the least, I thank my husband, Anand, whose wholehearted support and encouragement has allowed me the space and time to complete this focus.

With Regards,

DR. MANDAKINI PARIHAR MD, DGO

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COMBINED HORMONAL CONTRACEPTIVES – AN UPDATE

Editors – Dr. Suchitra Pandit and Dr. Mandakini Parihar

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Condom

In 1932 the London Rubber Company became Europe's first manufacturer of latex condoms, the Durex.

Oral Contraceptive Pill

In 1960, The G. D. Searle Drug Company received US FDA approval for Enovid - the first birth control pill that contained 9.85 milligrams (mg) of the progestational hormone norethynodrel and 150 micrograms (μg) of the estrogenic hormone mestranol—about 10 times the progestin and 4 times the estrogen contained in today's pills.

Minipill

In the early 1970s, the "mini-pill," an oral contraceptive containing only progestin, was introduced.

Emergency Contraceptive

In the early 1970s, the Yuzpe regimen was developed by AA Yuzpe (1974) & it became the standard course of treatment for postcoital contraception in many countries in the 1980s. On July 28, 1999, the US FDA approved the prescription progestin-only Plan B (two 750 μg levonorgestrel pills)

Intrauterine Device

In 1929, Dr. Ernst Gräfenberg of Germany published a report on an IUD made of silk suture.

The first plastic IUD, the Marguiles Coil or Marguiles Spiral, was introduced in 1958. The Lippes Loop was introduced in 1962.

Dr Howard Tatum, in the USA, conceived the plastic T-shaped IUD in 1968.

Contraceptive patch

The US FDA approved Ortho Evra, the first skin patch containing norelgestromin and ethinyl estradiol for birth control in November 2001, developed by R. W. Johnson Pharmaceutical Research Institute.

Chapter 1

Meeting Contraceptive Needs – Emerging Family Planning Priorities in India



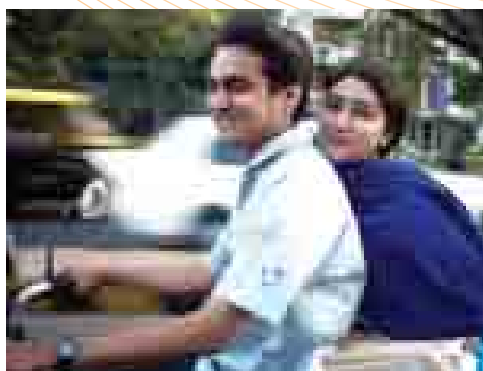
Dr. Dinesh Agarwal M.D.
National Programme Officer,
United Nations Population Fund

Current fertility scenario in India: Need for quality contraceptives services

The National Population Policy (NPP) 2000 sets out a goal of achieving total fertility rate (TFR) of 2.1 by 2010. The tenth FYP document aims for achieving TFR 2.3 by the end of plan period. Recently launched National Reproductive and Child Health programme phase 2 also spells out the similar goal.¹

As per release of census 2001 data, there is very little decline in TFR, since the 1991 census results. It has been estimated to be 3.04, only marginally lower than census 1991 estimates of 3.07. Researchers like Guilimoto et al (2002)² have also worked on district level estimates of TFR using reverse survival techniques using 0-6 population data for census 2001. By this method, TFR during 1994-2001 has been estimated to be 3.16. Total fertility rates are almost stagnant in most of the states or declined by 0.1 points in some states during the period of 1998-2000 as per SRS. Two out of every five births in the year 2000 were births of third or higher order. The fertility decline is not uniform across the states and even amongst districts within the states.

One of the most proximate detriments of fertility is effective use of contraceptives.



There is a clear relationship between total fertility rate and contraceptive prevalence rate. As per NFHS-2, contraceptive prevalence rate for modern methods of contraception is only 48.2 percent with large inter state variations.³ Hence if India has to achieve the policy goal of TFR of 2.1 by 2010, and achieve population stabilization, clearly concerted programmatic interventions are required to improve contraceptive prevalence amongst eligible couples.

India claims to be the first country in the world to launch a national programme to limit population growth by making contraceptive services available. The programme has since undergone many changes in the approach and thrust areas including the period during emergency, which is widely regarded as a period of “coercion” in family planning. The post

Table 1: Total Fertility Rate (TFR) and projected number of years to reach replacement levels: Major states of India

State	TFR 2002 SRS	Mean fall during last 10 years	Years required to achieve TFR of 2.1	Expected TFR in 2010
Andhra Pradesh	2.2	0.60	2	1.8
Assam	3.0	0.61	15	2.5
Bihar *	4.3	0.23	98	4.1
Gujarat	2.8	0.41	17	2.5
Haryana	3.1	0.80	12	2.5
Himachal Pradesh	2.1	0.82	0	1.8
Karnataka	2.4	0.57	5	1.8
Kerala	1.8	0.00	0	1.8
Madhya Pradesh *	3.8	0.44	39	3.4
Maharashtra	2.3	0.74	3	1.8
Orissa *	2.6	0.80	6	2.0
Punjab *	2.3	0.80	2	1.8
Rajasthan *	3.9	0.65	28	3.4
Tamil Nadu	2.0	0.13	0	1.8
Uttar Pradesh *	4.4	0.84	27	3.7
West Bengal	2.3	0.82	2	1.8
All India	3.0	0.64	14	2.5** (2.7)
Mean for EAG	4.1	0.59	33	3.6

*EAG states ** State-weighted average

Source: Prof. Mari Bhat, Institute of Economic Growth, Delhi, 2005

Cairo “paradigm shift” in the national programme has been major development at policy level and guided the design of interventions. It has been envisaged that a client centered, need based and quality oriented programme will effectively help couples and individuals to achieve their reproductive intentions.

In Bangladesh, total fertility rate has dropped by more than 50 percent, from nearly 7 per woman in the mid 1970s to 3.3 in the mid 1990s. This can be largely attributed to a quantum jump in the use of modern contraceptive methods from 7 percent to 43 percent in 1999-2000. Thus an impressive reduction in fertility has been achieved through provision of quality contraceptive services.

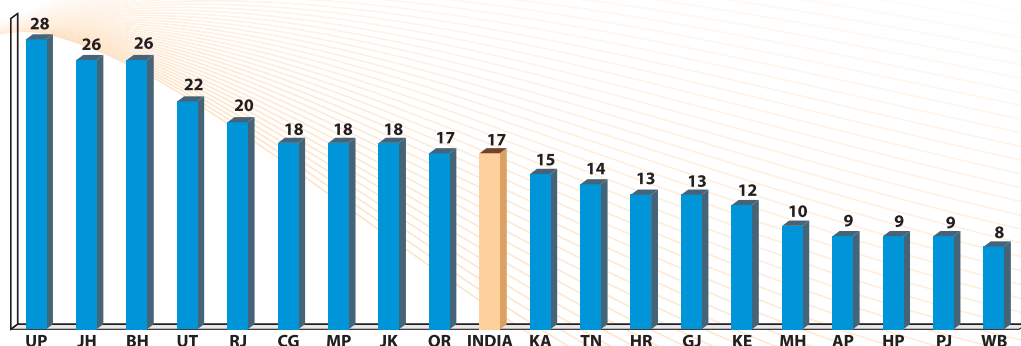
Contraceptive prevalence is influenced by two factors: demand for fertility regulation and use of contraceptives to meet such demand. The demand will be influenced by socio-economic and cultural factors and

the perceived costs and benefits of having children, and couples would demand contraception, if low fertility rates were considered beneficial. The programmes are supposed to meet this demand. However, the programme also seeks to generate demand in India.

Contraceptive Service Delivery: Key barriers

The health care delivery system has witnessed a rapid expansion of primary health care institutions during the last few decades. Over the years programmatic interventions have largely focused on improving access and quality of contraceptive services. However, despite policy and programme thrust on contraceptive access, unmet need for family planning remains high. As per NFHS-2, nearly 16 per cent of married women have unmet contraceptive need: 8.3 per cent for

Unmet need for family planning by state



Source: RHS 2002

spacing and 7.5 percent for limiting. Unmet need is much higher for women with one living child and for women with six or more living children. Rapid HH surveys for districts being conducted periodically also reported high unmet need for contraceptives (Fig. 1).

One of the major barriers also pertains to limited knowledge of contraceptives. Though large scale datasets indicate near universal knowledge of at least one method of contraception, certain aspects of knowledge such as dosage regimens, side effects and follow-up care are poor. There are rampant myths and misconceptions about spacing methods and also about male sterilization. A study conducted in the state of Karnataka, reported that while 56 percent of women and 61 percent of interviewed men were aware of reversible methods, a much smaller proportion, 31 percent women and 52 percent men knew about at least one service outlet for reversible methods.⁴

The Indian Family Planning programmes offers limited choices. In fact family planning users and providers have been calling for more choices. They want to have contraceptive methods that provide highly effective protection and at the same time cause fewer side effects, cost

less and are easier to use. Several methods available in other countries i.e., injectable contraceptives, implants etc are not offered in the national programme.

Poor counseling on contraceptives by providers further compromises the limited choice of methods. Findings from RCH HH survey indicate that only one third of sterilization users, less than half of IUD users and fewer than one fourth of pill users were informed about side effects before accepting the method⁵. It is very well known that women informed about side effects at the time of contraceptive initiation, are more likely to use contraceptives for longer duration, thus reducing method discontinuation significantly.

Low availability of contraceptive services also impact utilization. As per RCH facility survey, only 16 percent of PHCs had physicians trained in conducting sterilization and only two-thirds had at least one para-medical staff trained in IUD insertion. In such a scenario even if couples are keen to accept a contraceptive, their demand largely remains un-addressed as the system is unable to cater to their needs.

Poor quality of services is also an important barrier. Though several training programmes in the past have attempted to enhance

skills of providers in IUD insertion, as per a study, the majority did not feel confident about actually inserting an IUD in field settings and showed little awareness of the precautions to be taken. Concerns have been raised about the poor quality of pre-service training for ANMs and opportunities for hands-on skill development.

Access for sterilisation services at sub-district facilities on a regular and assured basis remains a major concern. In many states sterilisation camps rechristened as “RCH camps” are major sources of services. Though the camps are organized round the year the intensity of services increases during six months after the monsoon season. Invariably providers are drawn from the district hospitals, who have to complete their routine clinical workload, before heading to conduct sterilisation surgery at sub district facilities. In many instances clients have to wait for a long time, nothing by mouth, for the team to arrive at the campsite. The Government of India has updated standards for sterilisation. However, reports from the field indicate inability of providers to adhere to these guidelines. As per a study from the State of Uttar Pradesh,⁶ conducted in 1999, failure rate of 47 percent was reported, although internationally acceptable failure rate is only 0.5 percent. Nearly 30 percent failures were reported within three months of operation, which may be due to pre-existing pregnancy missed out during pre-operative examination. There are several instances of putting pressure on surgeons for doing more than the prescribed number of 20 operations per team per day. Service providers from other EAG States will vouch for similar situations in their districts.

Honorable Supreme Court has also taken cognizance of lack of skills amongst providers of sterilization services and

directed states to introduce a system having an approved panel of doctors and limiting the persons entitled to carry on sterilization procedures in the states to those doctors whose name appears on the approved panel. The Honorable Court has also directed that the criteria for inclusion of names of doctors on such a panel be laid down by GOI as indicated subsequently. The Court also directed the states to prepare and circulate a checklist that every doctor will be required to fill before carrying out sterilization procedure in respect of each proposed patient.⁷ Clearly such directions have emerged from the need to improve service quality of the sterilizations.

Prevailing gender inequalities also act as a barrier in contraceptive use. Most men do not come forward to take responsibility for contraceptive use or will approve of contraceptives after the second or third child. In the recent past an attempt has been made to offer non-scalpel vasectomy services through a network of institutions. In some of the states the acceptance of NSV is highly encouraging, although more needs to be done to train service providers in NSV and make these services available on a regular basis at the peripheral facilities.

Changing programme scenario Post-Cairo: Initiatives and results

The International Conference on Population and Development at Cairo in 1994 provided impetus for a “paradigm shift” in the Indian programme. In RCH Phase I, focus has been on assessing needs of community through Community Needs Assessment Approach and organizing service delivery interventions to meet contraceptive needs.

There is consensus, that despite huge investments in training of health care

providers in assessing community needs, development of service delivery work plans and monitoring service quality the situation is far from satisfactory in many states of the country. Similarly, early assessments show that the Community Needs Assessment Approach is yet to become fully operational in many parts of the country and its implementation varies across districts within each state, as well as across states.⁸ Many states continue to impose targets, setting local goals based on the previous year's centrally assigned targets.⁹ In many states, the involvement of women and other stakeholders in community needs assessment was reported to be minimal. Moreover, the data generated using community needs assessments have not yet been properly used for setting local goals,¹⁰ nor have they been used for making midcourse corrections.¹¹

Quality of contraceptive services remains a concern. Field level enquiries indicate that much needs to be done at the level of sub-centers and PHCs in terms of improving privacy and confidentiality, quality of client provider interaction and follow-up for contraceptives.

Critical issues of service quality and access that affect method use include availability of skilled providers at different levels of care. The providers should not only have clinical skills, but also skills in counseling to help clients about voluntary and informed decisions, about the number of children they would like to have and the contraceptive method they will like to use. Counseling is a key component in follow up care, and also in relation to prevention of STIs in the era of HIV/AIDS.

RCH Camps are considered as a major source of service for contraceptives. Invariably service providers tend to disregard women's needs for privacy and are uncaring about

women's dignity in these camps which are held at peripheral facilities. Most providers are not clued about "standards for male and female sterilization" released by the GOI. There are no mechanisms to monitor service quality in FP camps organized at clinic and outreach settings.

Follow-up is a major quality element. Data from NFHS-2 indicate that post-acceptance follow-up services are also limited, especially in the case of reversible methods. Nationally, for example, data from NFHS-2 show that there are four out of five sterilization users and two in five users of other modern methods who received follow-up services.¹² Data from the Reproductive and Child Health Survey-1, however, indicate that a much smaller percentage of women (only one in four) received a follow-up visit from a health worker after accepting the method – 27 per cent in the case of sterilization, 13 per cent for IUD and 7 per cent for pills. In many states, fewer than one in ten women reported receiving a follow-up visit.¹³ It is commonly observed that auxiliary nurse-midwives do not maintain their registers adequately to follow up users and lack a clear idea of how many have continued/discontinued the method.¹⁴

Thus though the programme was set out to assess client needs and organize services so as to meet the needs, somewhere down the line the capacity of the system to organize services seems to be constrained. The intensity of programme efforts is a critical factor to service the unmet needs of the clients.

Framework for strengthening interventions

The policy support for attaining the goal of population stabilization is clearly articulated in different policy and plan documents.

The RCH 2 programme proposes a mix of interventions to promote access and service quality so as to achieve the programme goal. However, much needs to be done in order to reach out to millions of couples, with unmet demand. Cutting down on unwanted pregnancies will also result in reduction in the number of maternal deaths and contribute to achieving MDGs.

Another area that deserves consideration relates to expanding method choices by addition of new methods in the programme. There is empirical evidence to suggest that addition of a new method will increase contraceptive utilization. As quality improves and more methods are introduced, more couples tend to use methods. For each method introduced, contraceptive prevalence increases by 3.3 percentage points. Recent studies suggest that 28 percent of Indian women do not want more than two children and 9 percent of all recent births/pregnancies are

unplanned. Further, 13 percent reported that they would like to wait for 2 yrs before bearing another child. Addition of new methods in the programme will allow the unmet demand of more couples to be satisfied.

Private sources are emerging as a major provider for reversible methods. As per rapid HH survey 2002,¹⁵ 52 percent of IUD acceptors sought services from private sources. Similarly there are encouraging trends for use of condoms and oral pills especially in social marketing brands. There is need to tap private sector potential through appropriately designed programmatic interventions adopting social franchising techniques. Grouping existing private providers under a brand, supported by training, brand promotion and supplies is a potentially important way of improving access to and quality of services. In a recent study from Nepal,¹⁶ it was shown in a quasi-experimental design, that satisfaction and utilization of reproductive health services by the clients was higher at the health establishments that were franchised as compared to the non-franchised ones.

A complex set of social, cultural and economic factors shapes and constrains social worlds in which adolescents struggle to make choices in matters of reproduction and contraceptive use. They invariably lack information on the contraceptives, although they often engage in activities which put them at the risk of unwanted pregnancy and/or infections. Thus programmes should clearly chalk out strategies to reach out to adolescents so as to service their contraceptive needs.

Quality of care in the family planning programme deserves priority attention. There is a need to set up mechanisms to regularly monitor service quality in family planning camps. Also programme managers



should use a monitoring checklist to assess service quality during routine field visits. This will also entail investments in terms of development of standards of care/guidelines and capacity building of service providers in adherence with standards and guidelines.

Conclusion

Over the years there has been significant increase in contraceptive use in India. However, addressing contraceptive needs of a sizable proportion of women and men and improving quality remains a major challenge. The policy planners, programme managers and service providers have to address some of the barriers. Similarly there are areas that need programmatic and research attention.

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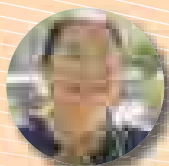
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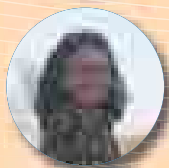
Chapter 2

Helping family planning programs work



Dr. Sadhana Desai

Convenor RCH
Past President FOGSI

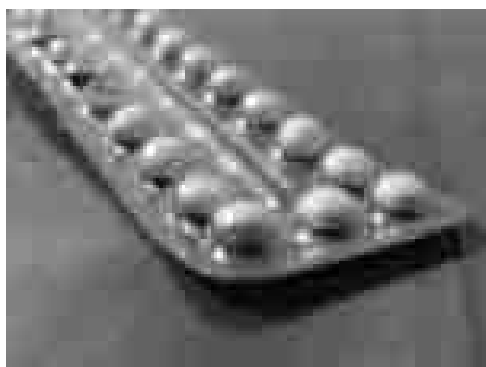


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Over the past 30 years, family planning programs have helped millions of people to have the smaller families that they want. However, there still exists a vacuum in the appropriate availability of all options and hence there is a large unmet need, especially in our country. It is estimated that there are more than 100 million women with an unmet need of contraception all over the world, and 35 million of these women are in India alone. This gives the extent of our problem and why we need to address this issue on a priority basis. The concept of “providing information about and access to a wide range of appropriate family planning methods” remains important today and adequate counseling with greater awareness will help in increasing the acceptability and usage.

What makes a family planning program work?

There are 10 key lessons about what makes programs succeed, based on a consensus of opinion among respondents to a new survey and a review of family planning research and program findings. FOGSI and GOI and all NGO's should work towards these goals



to make all forms of contraceptive options available and workable.

- 1. Family planning demand:** Given the opportunity, people choose contraception because it meets their personal needs.
- 2. Contraceptive access:** Successful programs offer services not only in clinics but also in retail outlets, community centers, places of employment, and people's homes.
- 3. Choice of Contraceptive access:** Offering a variety of methods helps to meet people's diverse needs and helps programs serve the changing needs of women and men over their reproductive lifetimes. (**Cafeteria approach**)

4. **Client-centered quality:** Clients are more likely to be satisfied to continue using family planning if they are able to make informed choices in a climate of respect for their needs and decisions.
5. **Communication.** Communication campaigns have helped millions of people become more aware of family planning and better informed about modern contraceptives.
6. **Well-trained providers.** Programs that train their staffs well are better equipped to meet their client's needs. Strengthening the technical and interpersonal skills of family planning providers enhances the quality of care and thus increases client's satisfaction with services. Counseling is important.
7. **Program leaderships.** Most successful programs have strong and stable leadership, and have brought services to the less educated and the poor as well as the middle class and to hard-to-reach rural areas as well as cities.
8. **Research and evaluation.** Analyze their performance improve their performance. Pilot projects, experiments, surveys, evaluation, and other studies guide the development of the most successful programs.
9. **Political commitment.** Strong endorsement both from the top of government and from community leaders.
10. **Financial resources.** Well-funded family planning programs accomplish more and accomplish it better.

Challenges and objections to contraceptives

Scientific research does accept that there is an element of risk inherent in each method and weighs it against possible benefits

and the efficacy level of the method. The campaign for the right to control one's body and fertility has raised several different issues, including the right to safe contraception and freedom from coercion in deciding how many children to have. It has also challenged the state for looking at people merely as numbers to be controlled and for treating women as wombs.

How can proper measures be taken to improve awareness and acceptability?

1. Satisfy the remaining unmet need for family planning among millions of married women who want to avoid pregnancy now;
2. Extend information and services to the young and the unmarried and to men;
3. Offer broader reproductive health services that also address issues of safe childbirth, abortion, AIDS and other sexually transmitted diseases.
4. Generate the resources needed to support and sustain high quality family planning services.

In the last 30 years the percentage of couples in developing countries using contraception has risen fivefold, from less than 10% in the 1960s to over 40% today. *Among the developing countries, contraceptive use generally is at the highest levels in countries that are most economically developed and at the same time have the strongest family planning programs.* This is lacking in our country's policy and that is where FOGSI can help actively. And it is important to remember that no single formula for the design of family planning programs suits all countries or cultures. Young people have been largely left out

of the family planning revolution. Many people think that providing family planning services to youth will promote promiscuity, even though there is no evidence of this.

It is of vital importance that the youth of today be educated and made aware of the different types of contraception and scientifically dispelling all their myths and disbeliefs. Successful programs reach out to young people on their own turf- at schools, recreational centres, work sites and on the street. With this year dedicated to the “Year of Gen Next”, we are hopeful that the things will begin to see a change for all and India in particular.

FOGSI can help by

1. Helping in authentic and appropriate clinical trials
2. Increasing awareness of various contraceptives amongst doctors and para-medical staff
3. Initiating proper counseling methods as per the WHO guidelines
4. Creating awareness amongst people by appropriate health care articles and programs
5. Incorporating Family Welfare activities in the RCH program by the GOI and helping people make informed choices.
6. Creating awareness about the various methods of contraception available and widening the basket of choices.
7. **Working with the GOI and starting Private Public Partnership programs to reach the common goal of Population Stabilization.**

It is important to remember that “Targets or quotas for the recruitment of clients should not be imposed on family planning providers; over the long term, meeting

the unmet need for information and services is the best way to achieve national demographic goals”

Awareness can be increased by:

1. Satisfying the remaining unmet need for family planning among millions of married women who want to avoid pregnancy now
2. Extending information and services to the young and the unmarried and to men
3. Offering broader reproductive health services that also address issues of safe childbirth, abortion, AIDS and other sexually transmitted diseases.

Communication Campaigns

In family planning programs, communication campaigns play many roles. They make people aware of modern contraception, its proper use, and where to find services. They counter myths, dispel rumors, and correct misinformation about modern contraceptives and family planning

Any successful program needs all of the following:

1. *At the service delivery level:*
 - a. Convenient access to contraceptive services
 - b. Choice of a range of contraceptive methods
 - c. High-quality, client-centered services
 - d. Sustained information, education, and communication
 - e. Trained personnel
2. *At the program administrative level*
 - a. Stable program leadership
 - b. Capable of strategic management
 - c. Research and evaluation

3. *At the government policy level*
 - a. Political commitment
 - b. Adequate financial support

Conclusion

No single formula for the design of family planning programs suits all countries or cultures. Family planning programs must do things well to succeed. Among the developing countries, contraceptive use generally is at the highest levels in countries that are most economically developed and at the same time have the strongest family planning programs.

Still the experiences of programs during the last 30 years have yielded valuable lessons. Family planning works best when it provides people with full information and a choice of services in a climate of respect. Government goals and projections may be an important part of national development planning. But setting targets for contraceptive “acceptors”

is not the road to family planning success. Rather, if people are given the opportunity, they choose family planning when it meets their needs.

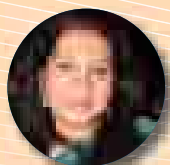
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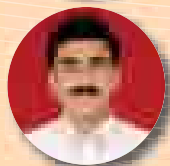


Chapter 3

Newer Progestins in Contraception



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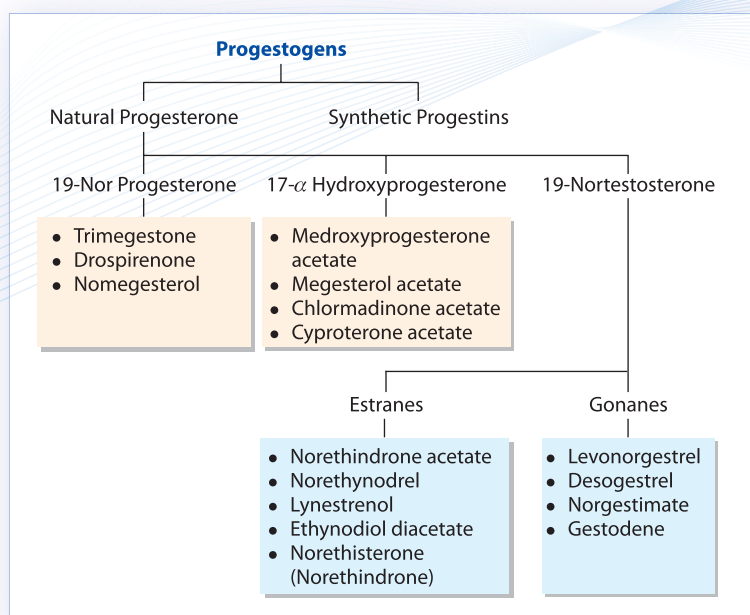
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The progestins or progestational agents used in OCs have a vital role in suppressing ovulation. Over the years, several newer and improved progestins have been developed with a view to improve the selectivity of progestational action and to minimize interaction with other steroid receptors that result in undesirable effects. The ultimate objective of developing a progestin is to have an agent that would resemble the naturally secreted progesterone in terms of

its progestational action.¹ The progestins used in OCs are classified as shown below.

In terms of progestins in OCs, there have been two major advances over the years²:

- A 10-fold reduction in the dose of the progestin
- Introduction of more selective progestins that minimize androgenic side effects while improving contraceptive efficacy.



Evolution of Newer Progestins

The older progestins synthesized in the 1960s and 1970s were designed to be used as contraceptives and hence the major target for their design was the antigonadotropic action. The newer progestins developed in the last two decades were designed with a view to create an “ideal progestin”.

Generations of Progesterones

1. First generation progestin; – Medroxyprogesterone acetate
2. Second generation progestin; – Levonorgestrel
3. Third generation progestin; – Desogestrel, Gestodene, Norgestimate
4. Anti-androgenic progestins; – 4th generation Progesterone

The newer progestins have no androgenic, estrogenic or glucocorticoid activity. They are referred to as pure progestational molecules as they bind almost exclusively to the progesterone receptor (PR) and do not interfere with other steroid receptors.³

New Progestins (4th Generation Progesterone)

- Dienogest (DNG)-(α-19-nortestosterone)
- Drospirenone (DRSP)
- Nestorone (NES)
- Nomegestrol acetate (NOMAC)
- Trimegestone (TMG)

The most recent progestin developed for use in OCs, drospirenone,³ has properties similar to progesterone itself (progestational action, antiandrogenic action and anti-

mineralocorticoid action). Thus it not only provides a high degree of contraceptive efficacy but also improves mood changes associated with menstruation, provides good cycle control, does not cause metabolic side effects such as dyslipidemia or glucose intolerance, does not cause significant bloating and weight gain (in fact it results in weight loss) and causes a small decrease in blood pressure. Thus, drospirenone-based OCs are a true advance in oral contraception, overcoming the limitations of the existing and widely used OCs and improving the quality of life and well-being.⁴

Clinical properties

1. Progestogenic

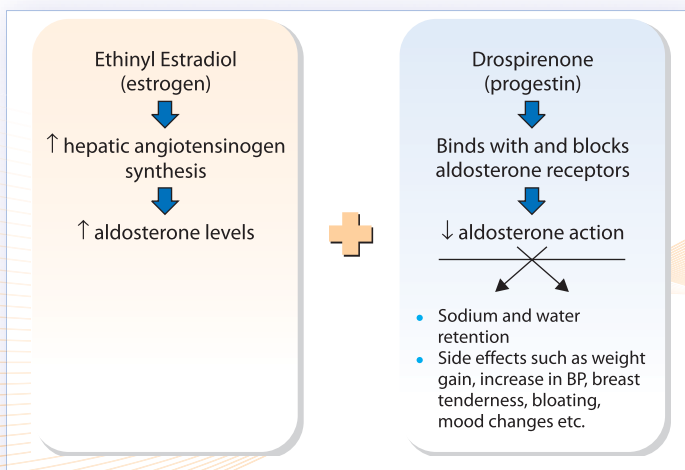
- Antigonadotropic action Inhibits ovulation: Contraceptive efficacy
- Inhibits estrogen-induced proliferation of endometrium – Decreased menstrual bleeding
- Transformation of cervical mucus to thick and viscid consistency- inhibits sperm penetration: additional contraceptive action

2. No Androgenic Action

- Does not cause oily skin or acne
- Does not promote weight gain
- No adverse effect on lipid profile
- No adverse effect on glucose tolerance

3. Anti-mineralocorticoid

This activity of drospirenone distinguishes it from other progesterone derivatives. The affinity of drospirenone for the mineralocorticoid receptor is about 5 times that of aldosterone. Estrogen increases the hepatic synthesis of angiotensinogen. This results in increased formation of angiotensin II and



aldosterone. The increased aldosterone secretion causes retention of sodium and water. This leads to increase in weight and blood pressure, breast tenderness, bloating etc. Due to antialdosterone property of drospirenone, body weight is maintained and increase in BP is prevented and also other fluid retention-related symptoms are improved.

4. Anti-androgenic

Drospirenone blocks the binding of androgen to its receptors at site like sebaceous glands, hair follicle etc. thus it effectively improves acne and hirsutism, which is beneficial in young women and adolescents.

Moreover, it also helps in regularizing menstrual cycles and improving acne and hirsutism in women with PCOS. Ethinyl estadiol increases the synthesis of SHBG by the liver; this will lower the free circulating androgen levels, thus decreasing seborrhea, acne and hirsutism.

In women with PCOS

- Decreases the LH levels and corrects LH:FSH ratio
- Decreases androgen levels
- Improves acne & hirsutism
- Regularizes the menstrual cycle

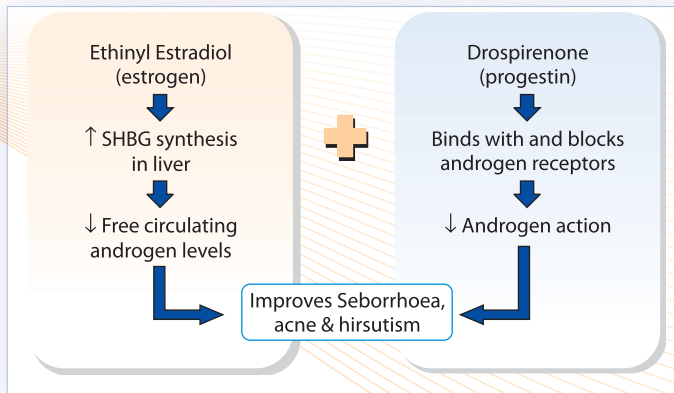
Drospirenone also increases HDL-C and decreases LDL-C levels in blood.

5. No effect on Glucocorticoid Receptors

- No interference with glucose tolerance
- May not adversely effect bone mineral density

6. No anti-estrogenic action

- Does not decrease estrogen-induced increase in sex hormone binding globulin (SHBG) levels
- Therefore no increase in free androgen levels
- Minimal changes of androgenic effects such as seborrhoea, acne etc.



Clinical Experience – Drospirenone +EE

Large-scale studies have been undertaken to evaluate the efficacy and safety of the combination of ethinyl estradiol (30 mcg) + drospirenone (3 mg) (EE + DRSP) in women desiring contraception as well as in those with acne, hirsutism, PCOS and premenstrual dysphoric disorder. This combination has been used by over 4 million women worldwide and it is the most widely used contraceptive. The result of the clinical studies and the worldwide clinical experience confirm that EE + DRSP is an effective and well-tolerated OC formulation.⁵

The highlights of the clinical studies are as follows:

- EE + DRSP has a high degree of contraceptive efficacy along with other beneficial actions such as improvement in the feeling of wellbeing, decreased incidences of acne, seborrhea and hirsutism, and reduction in body weight.
- Cycle control has been excellent with minimal effect on carbohydrate metabolism.

- Improvement in acne, seborrhea and hirsutism is similar to that seen with a cyproterone acetate containing preparation.
- Blood pressure remains unchanged.
- The combination has been shown to increase HDL-cholesterol and decrease LDL-cholesterol.
- Drospirenone and ethinyl estradiol have a favourable effect on body weight as compared to desogestrel containing pills.
- Also used in treatment of Premenstrual Dysphoric Disorder (PMDD).

It is seen in a survey that those women who were put on Drospirenone/EE combination for PMDD, showed a significant reduction in total record of severity of problems (DRSP) scores.⁵

- **Premenstrual Syndrome (PMS):** Many women face symptoms of tender breast, food craving, fatigue, irritability, depression and mood swings. A combination of drospirenone 3mg plus EE 30 mcg significantly reduced these symptoms.⁶
- **Acne:** The combination of drospirenone and EE evaluated for treatment of

mild to moderate acne showed 62% reduction of acne lesion count and 25% reduction of seborrhea.⁷

- **Hirsutism:** This combination is a therapeutic choice among other options in PCOS women with hirsutism.⁸
- **Polycystic Ovarian Syndrome :** The efficacy of this combination has been evaluated in many studies, and it was observed that a significant improvement after 6 cycles was seen in Ferriman – Gallwey (F.G.) score, body mass index, waist/hip ratio, serum levels of testosterone, SHBG, immune reactive insulin (IRI), glucose, the free androgenic index, and insulin resistance (HOMA-IR).⁹
- **Post Menopause:** A Combination of drospirenone and EE has been evaluated for use for menopausal syndrome and the combination has been shown to be beneficial in relieving hot flashes, hypertension and has a protective effect on endometrial hyperplasia.¹⁰

Prescribing Information

The COC was approved by FDA in the dose of 3 mg drospirenone with 30 mcg ethinyl estradiol.

It is administered in a 1 day, 21/7 regimen i.e. 21 days of active pill started from day 1 to 21 followed by 7 days of hormone free interval. The pill should be taken at the same time every day, preferably in the late evening. It becomes effective as a contraceptive after a minimum of 7 days consecutive ingestion.

Other regimens with a change of estradiol dosage have also been formulated as 21 days and 24 days regimen.

Conclusions

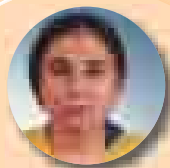
The modern women today need a method which is safe and free of side effects and has a beneficial beautification effect. The combination of drospirenone with ethinylestradiol has made a new promise for such women.

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Chapter 4

WHO Eligibility Criteria for Hormonal Contraception



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Every year approximately 210 million women become pregnant and as many as 80 million of these pregnancies are unplanned. Since the introduction of oral contraceptives, research has focused on modifying the dosage of estrogen and progesterone formulations to improve safety and acceptability.

The 'medical eligibility' criteria for combined hormonal contraceptive use by WHO provides guidance regarding "who" can use contraceptive methods safely and the selected practice recommendation for contraceptive use, which provides guidance regarding "how" to use contraceptive methods safely and effectively. It offers guidance on whether a person with a specific health condition can safely start to use a specific contraceptive method or, if she or he develops a health condition, can continue to use the method safely.



The medical eligibility criteria for contraceptive use were first published in 1996 and provide detailed guidance regarding who can use contraceptive methods safely. In October 2003 in WHO headquarters at Geneva, Switzerland it was

updated. In this meeting the Expert Working Group addressed contraceptive use in situations involving or related to HIV/AIDS, and clinical depression in women. They considered whether certain drugs interact with hormonal contraceptives. They issued new family planning guidance, including the following:

- Most women with HIV infection generally can use IUDs.
- Women generally can take hormonal contraceptives while on antiretroviral (ARV) therapy for HIV infection although there are interactions between contraceptive hormones and certain ARV drugs.
- Women with clinical depression usually can take hormonal contraceptives.

The recommendations are provided by assigning Categories 1 to 4 – with Category 1 indicating that method use is unrestricted and Category 4 indicating that method use presents an unacceptable health risk. Category 2 is assigned when advantages of use are deemed to generally outweigh risks and Category 3 is assigned when risks of use usually outweigh advantages.

Table 1: Category description for WHO eligibility for contraceptive usage.

Category	Description	Interpretation When Clinical Judgement Is Available	Interpretation
1	No restriction for the use of the contraceptive method.	Use the method in any circumstances.	 Use the method.
2	The advantages of using the method generally outweigh the theoretical or proven risks.	Generally use the method.	
3	The theoretical or proven risks usually outweigh the advantages of using the method. Safe use requires careful clinical judgement and access to clinical services.	Use the method not usually recommended unless other more appropriate methods are not available or not acceptable.	 Do not use the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used.	Method not to be used.	

Source: World Health Organization, 2000 (51)

Table 2: Indications for Combined Contraceptive usage.

No restriction of use: WHO category I

- Menarche to 40 years
- Obesity
- History of pre-eclampsia
- History of ectopic pregnancy
- Postpartum 21 days, non-breast feeding
- Breast feeding more than six months postpartum
- Post-abortion
- Irregular menstrual bleeding/dysmenorrhoea
- Iron deficiency anaemia
- Past history of PID /STD
- History of gestational diabetes
- Cervical erosion
- Fibroids
- Pelvic inflammatory diseases
- Gestation trophoblastic disease
- Varicose veins
- Thyroid disease
- Previous history of liver disease (not active or carrier)
- Tropical diseases

Indications with caution : WHO category II

- Uncomplicated valvular heart disease
- Mild hypertension
- Age more than 40 years
- Smokers less than 35 years, light smoker more than 35 years
- Thalassaemia
- Breast feeding less than six months postpartum
- Recent history of jaundice
- Sickle cell disease
- Diabetes, uncomplicated
- Undiagnosed breast disease
- Gallbladder disease

Table 3: Contraindications: WHO category III and IV

- Pregnancy, lactation
- Thromboembolic disease
- Coronary occlusion, complicated valvular disease
- Atherosclerosis and stroke
- Uncontrolled hypertension
- Systemic lupus erythematosus
- Diabetic retinopathy or nephropathy
- Known or suspected breast carcinoma
- Past breast cancer
- Pre malignant and malignant changes of the uterus or vagina
- Smokers above 35 years of age
- Migraine with aura – as it increases risk of stroke requiring prolonged bed rest after major surgery
- Uncontrolled diabetes mellitus
- Severe depression
- Cholestatic jaundice
- Active liver disease
- Known hypersensitivity of EE or progesterone

Relative Contraindications

- Heavy smoker
- Lactation six weeks to six months postpartum
- Unexplained vaginal bleeding
- History of hypertension but BP less than 180 / 100
- Benign liver tumours
- Use of drugs interacting with OCs
- Hyperlipidaemia



WHO Eligibility

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
SMOKING		Evidence: COC users who smoked were at increased risk of cardiovascular diseases, especially myocardial infarction, compared with those who did not smoke. Studies also showed an increased risk of myocardial infarction with increasing number of cigarettes smoked per day.	
a) Age < 35 years	2		
b) Age > 35 years			
i) <1 5 cigarettes/day	3		
ii) >1 5 cigarettes/day	4		
OBESITY	2	Evidence: Obese women who used COCs were at increased risk of VTE compared with non-users. The absolute risk of VTE remained small. Data are limited regarding the impact of obesity on COC effectiveness.	
> 30 kg/m ² body mass index (BMI)			
BLOOD PRESSURE MEASUREMENT UNAVAILABLE	NA	Clarification: It is desirable to have blood pressure measurements taken before initiation of COC use. However, in some settings blood pressure measurements are unavailable. In many of these settings pregnancy morbidity and mortality risks are high, and COCs are one of the few methods widely available. In such settings, women should not be denied use of COCs simply because their blood pressure cannot be measured.	
CARDIOVASCULAR DISEASE			
MULTIPLE RISK FACTORS FOR ARTERIAL CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes and hypertension)	3/4	Clarification: When a woman has multiple major risk factors, any of which alone would substantially increase the risk of cardiovascular disease, use of COCs may increase her risk to an unacceptable level. However, a simple addition of categories for multiple risk factors is not intended; for example, a combination of two risk factors assigned a category 2 may not necessarily warrant a higher category.	
HYPERTENSION*			
For all categories of hypertension, classifications are based on the assumption that no other risk factors for cardiovascular disease exist. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive.			
a) History of hypertension, where blood pressure CANNOT be evaluated (including hypertension in pregnancy)	3	Clarification: Evaluation of cause and level of hypertension is recommended, as soon as feasible. Evidence: Women who did not have a blood pressure check before COC use had an increased risk of acute myocardial infarction and stroke.	
b) Adequately controlled hypertension, where blood pressure can be evaluated	3	Clarification: Women adequately treated for hypertension are at reduced risk of acute myocardial infarction and stroke as compared with untreated women. Although there are no data, COC users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive COC users.	

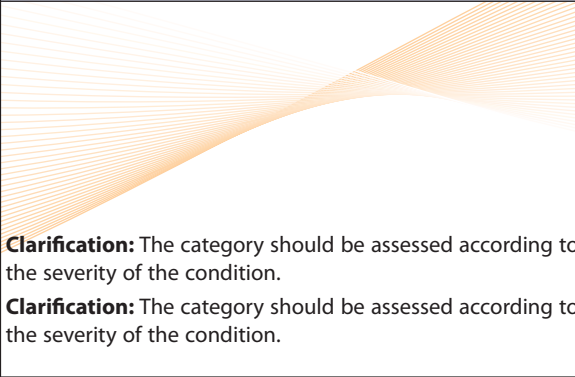
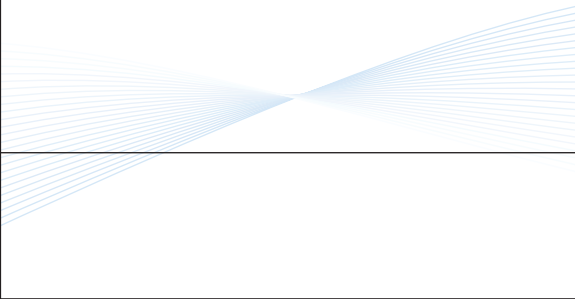
LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
HYPERTENSION (Contd.)			
c) Elevated blood pressure levels (properly taken measurements) i) systolic 140-159 or diastolic 90-99 ii) systolic ≥160 or diastolic ≥100	3	Evidence: Among women with hypertension, COC users were at increased risk of stroke, acute myocardial infarction, and peripheral arterial disease compared with non-users.	
	4		
	4		
d) Vascular disease	4		
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure is measurable and normal)	2	Evidence: Women who had a history of high blood pressure in pregnancy, who also used COCs, had an increased risk of myocardial infarction and venous thromboembolism, compared with COC users who did not have a history of high blood pressure during pregnancy. The absolute risks of acute myocardial infarction and venous thromboembolism in this population remained small.	
DEEP VENOUS THROMBOSIS (DVT)/ PULMONARY EMBOLISM (PE)*			
a) History of DVT/PE	4		
b) Current DVT/PE	4		
c) Family history of DVT/PE (first-degree relatives)	2		
d) Major surgery			
i) with prolonged immobilization	4		
ii) without prolonged immobilization	2		
e) Minor surgery without immobilization	1		
KNOWN THROMBOGENIC MUTATIONS (e.g., Factor V Leiden; Prothrombin mutation; Protein S, Protein C, and Antithrombin deficiencies)	4	Clarification: Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. Evidence: Among women with thrombogenic mutations, COC users had a two to twenty-fold higher risk of thrombosis than non-users.	
SUPERFICIAL VENOUS THROMBOSIS*			
a) Varicose veins	2		
b) Superficial thrombophlebitis	4		

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE*	4		
STROKE* (history of cerebrovascular accident)	4		
KNOWN HYPERLIPIDAEMIAS	2/3	Clarification: Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidaemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors.	
VALVULAR HEART DISEASE* a) Uncomplicated b) Complicated pulmonary hypertension, risk of atrial fibrillation, history of subacute bacterial endocarditis	2 4		
NEUROLOGIC CONDITIONS			
HEADACHES*	1	C	Clarification: Classification depends on accurate diagnosis of those severe headaches that are migrainous and those that are not. Any new headaches or marked changes in headaches should be evaluated. Classification is for women without any other risk factors for stroke. Risk of stroke increases with age, hypertension and smoking. Evidence: Among women with migraine, women who also had aura had a higher risk of stroke than those without aura. Among women with migraine, those who used COCs had a 2 to 4-fold increased risk of stroke compared with women who did not use COCs.
a) Non-migrainous (mild or severe)	1	2	
b) Migraine			
i) without aura	2	3	
Age < 35	3	4	
Age ≥ 35	4	4	
ii) with aura, at any age			
EPILEPSY	2	Clarification: If a woman is taking anticonvulsants, refer to the section on drug interactions. Certain anticonvulsants lower COG effectiveness.	
DEPRESSIVE DISORDERS			
DEPRESSIVE DISORDERS	1	Clarification: The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives. Evidence: COC use did not increase depressive symptoms in women with depression compared to baseline or to non-users with depression.	

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
REPRODUCTIVE TRACT INFECTIONS AND DISORDERS			
VAGINAL BLEEDING PATTERNS*			
a) Irregular pattern <i>without</i> heavy bleeding	1		
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1	Clarification: Unusually heavy bleeding should raise the suspicion of a serious underlying condition.	
UNEXPLAINED VAGINAL BLEEDING* (suspicious for serious condition) Before evaluation	2	Clarification: If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.	
ENDOMETRIOSIS*	1		
BENIGN OVARIAN TUMOURS (including cysts)	1		
SEVERE DYSMENORRHOEA	1	Evidence: There was no increased risk of side-effects with COC use among women with dysmenorrhoea compared to women not using COCs. Some COC users had a reduction in pain and bleeding.	
TROPHOBLAST DISEASE			
a) Benign gestational trophoblastic disease	1	Evidence: Among women with benign or malignant gestational trophoblastic disease, there was no difference in mean times to hCG normalization or incidence of postmolar trophoblastic disease for COC users compared to non-hormonal users.	
b) Malignant gestational trophoblastic disease	1		
CERVICAL ECTROPION*	1		
CERVICAL INTRAEPITHELIAL NEOPLASIA (CtN)	2	Evidence: Among women with persistent HPV infection, long-term COC use (≥ 5 years) may increase the risk of carcinoma in situ and invasive carcinoma.	
CERVICAL CANCER (awaiting treatment)	2		

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
BREAST DISEASE*			
a) Undiagnosed mass	2	Clarification: Evaluation should be pursued as early as possible. Evidence: Among COC users with a family history of breast cancer, there was no increased risk of breast cancer compared with non-COC users with a family history of breast cancer. Among women with BRCA1 mutations, COC users may have a small increased risk of breast cancer compared with non-users.	
b) Benign breast disease	1		
c) Family history of cancer	1		
d) Breast cancer			
i) current	4		
ii) past and no evidence of current disease for 5 year	3		
ENDOMETRIAL CANCER*	1		
OVARIAN CANCER*	1		
UTERINE FIBROIDS*			
a) Without distortion of the uterine cavity	1		
b) With distortion of the uterine cavity	1		
PELVIC INFLAMMATORY DISEASE (PID)*			
a) Past PID (assuming no current risk factors for STIs)			
i) with subsequent pregnancy	1		
ii) without subsequent pregnancy	1		
b) PID – current	1		
STIs*			
a) Current purulent cervicitis or chlamydial infection or gonorrhoea	1		
b) Other STIs (excluding HIV and hepatitis)	1		

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
STIs* (Contd.)			
c) Vaginitis (including trichomonas vaginalis and bacterial vaginosis)	1	Evidence: Evidence suggests that there may be an increased risk of chlamydial cervicitis among COC users at high risk of STIs. For other STIs there is either evidence of no association between COC use and STI acquisition or limited evidence to draw any conclusions.	
b) Increased risk of STIs	1		
HIV/AIDS			
HIGH RISK OF HIV*	1	Evidence: Overall, evidence is inconsistent regarding whether there is any increased risk of HIV acquisition among COC users compared with non-users.	
HIV-INFECTED	1	Evidence: Limited evidence suggests no association between COC use and changes in RNA levels or CD4 counts among HIV-infected women. There is also limited evidence showing no association between COC use and female to male HIV transmission, and mixed results regarding increased risk of HIV and herpes simplex virus (HSV) shedding among HIV-infected women using hormonal contraception.	
AIDS	1	Clarification: If a woman is taking antiretroviral (ARV) therapy, refer to the section on drug interactions. Because there may be drug interactions between hormonal contraceptives and ARVs, AIDS with ARV therapy is classified as Category 2.	
On ARV therapy	2		
OTHER INFECTIONS			
SCHISTOSOMIASIS			
a) Uncomplicated	1	Evidence: Among women with uncomplicated schistosomiasis, COC use had no adverse effects on liver function.	
b) Fibrosis of liver (if severe, see cirrhosis)	1		
TUBERCULOSIS			
a) Non-pelvic	1	Clarification: If a woman is taking rifampicin, refer to the section on drug interactions. Rifampicin is likely to decrease COC effectiveness.	
b) Known pelvic	1		
MALARIA	1		

LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
DIABETES*			
a) History of gestational disease	1		
b) Non-vascular disease			
i) non-insulin dependent	2		
ii) insulin dependent	2		
c) Nephropathy/retinopathy/neuropathy	3/4		
d) Other vascular disease or diabetes of > 20 years' duration	3/4	Clarification: The category should be assessed according to the severity of the condition.	
THYROID DISORDERS			
a) Simple goitre	1		
b) Hyperthyroidism	1		
c) Hypothyroidism	1		
GASTROINTESTINAL CONDITIONS			
GALL-BLADDER DISEASE*			
a) Symptomatic			
i) treated by cholecystectomy	2		
ii) medically treated	3		
iii) current	3		
b) Asymptomatic	2		
HISTORY OF CHOLESTASIS*			
a) Pregnancy-related	2		
b) Past COC-related	3		
VIRAL HEPATITIS*			
a) Active	4		
b) Carrier	1		
CIRRHOSIS*			
a) Mild (compensated)	3		
b) Severe (decompensated)	4		
LIVER TUMOURS*			
a) Benign (adenoma)	4		
b) Malignant (hepatoma)	4		

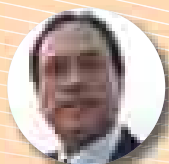
LOW-DOSE COMBINED ORAL CONTRACEPTIVES (COCs) ≤ 35 µg of ethinylestradiol		COCs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against STI/HIV.	
CONDITION	CATEGORY I= Initiation C=Continuation	CLARIFICATIONS/EVIDENCE	
ANEMIAS			
THALASSAEMIA*	1		
SICKLE CELL DISEASE	2		
IRON-DEFICIENCY ANAEMIA			
DRUG INTERACTIONS			
DRUGS WHICH AFFECT LIVER ENZYMES			
a) Rifampicin	3	Clarification: Although the interaction of rifampicin or certain anticonvulsants with COCs is not harmful to women, it is likely to reduce the effectiveness of COCs. Use of other contraceptives should be encouraged for women who are long-term users of any of these drugs. Whether increasing the hormone dose of COCs is of benefit remains unclear. Evidence: Use of rifampicin and certain anticonvulsants decreased the contraceptive effectiveness of COCs.	
b) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3		
ANTIBIOTICS (including rifampicin)			
a) Griseofulvin	2	Evidence: The contraceptive effectiveness of COCs was not affected by coadministration of most broad-spectrum antibiotics.	
b) Other antibiotics	1		
ANTIRETROVIRAL THERAPY		2	Clarification: It is important to note that antiretroviral drugs (ARV) have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available suggest that potential drug interactions between many ARVs (particularly some non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)) and hormonal contraceptives may alter safety and effectiveness of both the hormonal contraceptives and the ARVs. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as depot medroxyprogesterone acetate and norethisterone enantate) would be compromised, and these methods provide higher blood hormone levels than other progestogen-only hormonal contraceptives, as well as than combined oral contraceptives. Studies are underway to evaluate potential interactions between depot medroxyprogesterone acetate and selected PI and NNRTI drugs. Thus, if a woman on ARV treatment decides to initiate or continue hormonal contraceptive use, the consistent use of condoms is recommended for preventing HIV transmission and may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

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Chapter 5

Low dose oral contraceptive pill



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“*With the availability of wide range of contraception, in the twenty first century pregnancy should be by choice, not by chance.*”

Introduction

Combined oral contraceptive (COC) pills are a widely used, effective and reversible method of family planning worldwide. Although COC has been used by about 100 million women globally, the recent National Family Health Survey (NFHS-3) shows that only 3.1% of married Indian women have actually used it during 2005-2006. There is a wide gap between safety and efficacy records of COC and its acceptance by the Indian women. This remains a major concern for the policy makers worried about relentless population growth.

Why low dose pill?

For a long time researchers have been searching for a pharmacological agent which will effectively suppress ovulation without causing many side effects. Initial COC contained 150 microg of synthetic estrogen. Gradually it has been realized that many side effects are related to

estrogen, and they are dose related. The dose of estrogen was such a critical issue that scientists have worked hard to produce a pill, which contains the lowest possible effective dose of estrogen. COCs containing less than 50 microg ethinyl estradiol (EE) are known as low dose pills (LDP). High dose of progestins are also found to be responsible for other adverse effects. Search for new, safe progestins is also continued simultaneously. Basic questions after lowering the dose of both estrogen and progestins are – its efficacy, safety, side-effects, cost and compliance. Currently, COCs are classified into 3 groups:

First generation COC pill	Pills containing 50 microg or more EE
Second generation COC pill	20, 30 or 35 microg EE, and levonorgestrel or norgestimate
Third generation COC pill	20, 30 or 35 microg EE, and desogestrel or gestodene

Efficacy

Large number of clinical trials have documented the contraceptive efficacy of LDP, which is mostly related to correct use of pill-taking regimen.¹ Similar efficacy has been demonstrated while comparing

LDP containing 35 microg and 20 microg of EE. Cochrane review concluded that the available evidence is insufficient to determine whether triphasic COCs differ from monophasic COCs in their effectiveness, bleeding patterns or discontinuation rates. Monophasic pills are recommended as a first choice for women starting COC.²

Compliance

Satisfactory and long-term use of LDP depends on effective cycle control, and the incidence and severity of side effects. Of subjects who discontinued the pill during the course of a recent study, a majority listed "medical side effects" such as nausea, headache, and breakthrough bleeding as the reasons for discontinuation.³ In a randomized multicenter trial from Germany and Netherlands, the women received either 20 microg EE plus 150 microg desogestrel or 20 microg EE plus 100 microg levonorgestrel for six treatment cycles. The latter pill has higher discontinuation rate due to unacceptable vaginal bleeding.⁴ This irregular vaginal bleeding may have an adverse bearing for continuation of LDP in Indian women.

Adverse events

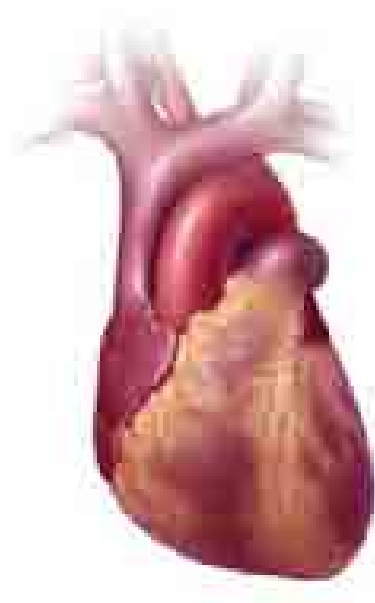
Venous thromboembolism

The relationship between COC and venous thromboembolism (VTE) generated great debate, and extensive research has been done to find out the association. Among users of COC, estrogen and progestin both increase the risk of VTE. Other co-factors are age, smoking, hereditary thrombophilias and diabetes etc. Women on COC experience VTE at a rate of 12 to 20 cases per 100,000 woman-years compared to 5 to 10 per 100,000 woman-

years in non-users (a 4-fold increased risk). It is very important to interpret this data keeping in mind the typical baseline risk of VTE associated with normal pregnancy (60 cases per 100,000 woman-years). Furthermore, although relative risk is 4-fold, the absolute risk is minimal – 1 per 10,000 woman-years of use. In 1995, World Health Organisation⁵ published higher occurrence of thromboembolic events with the third-generation progestins (desogestrel and gestodene) compared to second generation progestins. This publication generated the so-called "Pill Scare" of 1995, resulting in confusion among doctors and users alike. A subsequent study concluded that he previously reported increased VTE risk associated with third-generation OCs likely reflects age as an important confounding variable.⁶

Myocardial infarction

Incidence of myocardial infarction (MI) increases with age and in the presence of other well-documented risk factors (smoking, obesity, diabetes, and hypertension). Current use of COC is



associated with an increased risk of acute MI among women with known cardiovascular risk factors and among those who have not been effectively screened, particularly for hypertension.⁷ A meta-analysis of COC use in relation to myocardial infarction demonstrated that current COC users have 2.5 fold risk of MI.⁸ However, a population-based, prospective cohort study from Sweden over 11 years concluded that the use of COC is not associated with an increased risk of MI (most current users of OC were taking low-dose estrogen and second- or third-generation progestins).⁹

Stroke

Previous studies have linked the use of oral contraceptive agents to an increased risk of stroke, but those studies have been limited to COC containing more estrogen than is now generally used. A WHO study¹⁰ suggests that the incidence of ischemic stroke is low in women of reproductive age and any risk attributable to OC use is small. The risk can be further reduced if users are younger than 35 years, do not smoke, do not have a history of hypertension, and have blood pressure measured before the start of OC use. In such women, OC preparations with low estrogen doses may be associated with even lower risk. An Australian case-control study demonstrated that compared with past use, current use of the COC, in doses of 50 microg or less of EE, was not associated with an increased risk of ischemic stroke.¹¹

Coagulation and hemostasis

In a combined analysis, no consistent pattern emerged for any coagulation or fibrinolysis parameter with the exception of higher factor VII levels associated with third-generation formulations.¹² In a double-blind, randomized study the effects of two combined oral contraceptives containing 150 microg desogestrel and either 20 or 30

microg EE on hemostatic parameters were investigated in 1633 healthy women. The less-pronounced effect on hemostasis with the 20 microg EE preparation is reassuring with regard to thrombo-embolic risk in general. However, women with coagulation inhibitor deficiency should be advised not to use oral contraceptives.¹³

Carbohydrate metabolism

The progestin component of COC is responsible for most changes in carbohydrate metabolism. COC use can lead to increased levels of plasma insulin, insulin resistance, and relative glucose intolerance, which are not as great in women using the lower dose COC or formulations using the new progestins. COC use does not influence subsequent development of diabetes, but it may affect the control of diabetes.

Lipid metabolism

Estrogens usually increase high-density lipoprotein (HDL) and decrease low-density lipoprotein (LDL) and progestins tend to do the reverse (decrease HDL and increase LDL and total cholesterol). A study on the effect of two LDP, both containing 150 microg of desogestrel, but with 20 or 30 microg of EE as a whole be interpreted as beneficial. However, the clinical significance of these changes is uncertain.¹⁴

Cancer

One of the major concerns among the pill users is the risk of subsequent development of cancer, especially breast cancer. Recent data from the Oxford Family Planning Association contraceptive study was reassuring.¹⁵ In another study on UK cohort, oral contraception was not associated with an overall increased risk of cancer; indeed it was concluded that there may be a net public health gain.¹⁶

Non contraceptive benefits and side effects

There are several side effects and non contraceptive benefits of LDP depending on the composition and doses of the estrogen and progestogen components. These are discussed in other chapters.

Conclusions

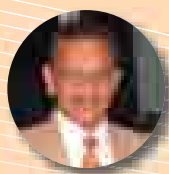
Overall the low dose pill maintained the efficacy like the older pill. Large studies also demonstrated good safety record. Largely the side effects are within acceptable limits. It also maintained the non-contraceptive benefits like the higher dose pill.

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Pill with Cyproterone Acetate



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The monophasic pill with CPA with good cycle control, low incidence of side effects and improvement in androgenic symptoms deserves more widespread use in androgenic oligomenorrhea with PCOS in women wishing contraception at the same time.

Cyproterone Acetate

Cyproterone Acetate is a progestin with antiandrogenic properties with weak glucocorticoid effect.^{1,2} Antiandrogenic action is through inhibition of 5- α reductase activity and blocking of androgen receptors. It is used in a contraceptive pill along with ethinylestradiol 35mcg. A clinical study shows a definite decline in hirsutism and acne. The main symptoms of hyperandrogenism are coupled with significant changes in androgenic markers.³

In women ovarian function is inhibited^{4,5} and ovulation suppressed. Cyproterone acts as a potent ovulation inhibiting contraceptive.⁶ CPA is 250 times more active than progesterone in Clauberg test.⁷ Inhibition of ovulation and cervical mucus changes by virtue of its strong progestational activity, CPA has proved its contraceptive properties in combination with ethinyl estradiol.

The maximal plasma levels are reached 3-

4 hours after oral administration. Excretion occurs via bile (70%) and urine (30%). Being lipophilic, plasma half life is prolonged in obese patients.

If higher dose of CPA is used in prostatic carcinoma, there is reduction in sexual drive in males and idiopathic precocious puberty in children.

PCOS

Polycystic ovarian disease is not an uncommon disorder seen in the reproductive age group. It is a disorder of uncertain etiology and presents with hyperandrogenism, anovulation and insulin resistance as the main features along with the typical polycystic ovaries, menstrual irregularities, infertility, hirsutism and acne. The clinical features of PCOS need careful evaluation and comprehensive management.

Pill with CPA

Pill with CPA can normalize the endocrine patterns in PCOS and improve androgenic symptoms.⁸ The combination gives a good cycle control.⁹ For long term use for 36 months without interruption, significant improvement in endocrine and clinical parameters have been noted.¹⁰

Hirsutism

Ethinyl estradiol along with Cyproterone acetate helps in correcting clinical and endocrinological abnormalities of PCOS. EE by way of increasing the SHBG levels and suppressing the LH, CPA by blocking the androgen receptors on sebaceous glands and hair follicle, brings down the hyperandrogenic manifestations of PCOS and corrects menstrual irregularities as well.

The Cochrane database systematic review quotes that Cyproterone acetate combined with estradiol results in a subjective improvement in hirsutism compared to placebo.¹¹

Pill with CPA is effective in hirsutism as there was a significant improvement in Ferriman-Gallwey score and rise in SHBG.¹⁶ CPA in 2 mg dose is as effective as higher doses in treatment of hirsutism as assessed by Hair shaft diameter, F-G score and linear hair growth.¹³ Comparative study of Pill with CPA and other anti androgens (Flutamide, Fenesteride) shows that Pill with CPA induces the quickest reduction in hair growth thus making it the better choice in ovarian and adrenal hirsutism in sexually active women because of steroid suppression and contraceptive effect.¹⁴

Acne

Effect of EE-CPA combination on acne is through reduction in sebaceous cell function and blocking of androgen receptors on sebaceous gland. EE-CPA combinations are widely regarded as the benchmark for treatment of acne.¹⁵ Pill

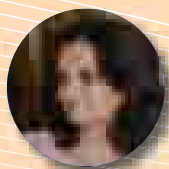
with CPA use in severe androgenisation yielded 90% success rate in control of acne lesions.¹² In comparison with the biphasic pill, EE with CPA combination shows significant progressive reduction in severity of comedones and pustules.¹⁷

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Chapter 7

OC Pills containing Drospirenone



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“Technology made large populations possible and large populations today make technology indispensable”

Joseph Krutch.

Introduction

Modern contraceptive methods represent more than a technical advance; they are the instrument of a true social revolution – the “first reproductive revolution” in the history of humanity, and an achievement of the second part of the 20th century, when modern, effective methods became available. The human population, which had more than tripled from 1.8 to more than 6 billion in just one century, is today being brought under control.

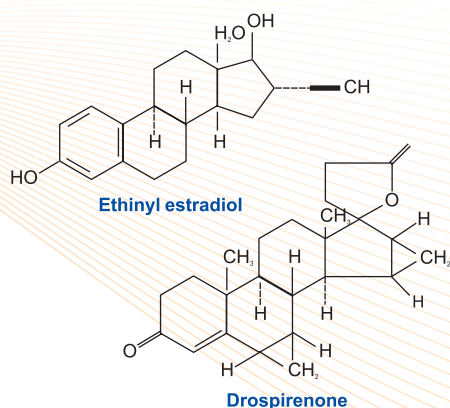
Hormonal contraception, the best known method, was first made available as a daily pill.

New oral contraceptives are being developed in order to improve tolerance while ensuring efficacy and good cycle control. Two approaches are commonly being investigated:

- to lower the steroid dose of both the oestrogen and progestogen components
- to utilize new progestogens with a more favourable pharmacological profile.

However, almost all synthetic progestogens currently in clinical use lack certain characteristics of natural progesterone and, therefore, there remains some potential for a better oestrogen/progestogen combination to be developed. Development of new progestogens with improved pharmacological activity is, therefore, an important aspect of current research. One such new progestogen is **drospirenone**, which is being developed for use in combined oral contraceptive preparations. This novel progestogen differs in important ways from other currently available progestogens and has a pharmacological profile that is very similar to natural progesterone.

In some women, the use of conventional oral contraceptives can result in fluid retention and associated symptoms such as oedema and weight gain. This aspect of oral contraceptive use is particularly important, since, along with cycle control, weight gain is a major reason for women discontinuing, or not initiating, oral contraceptive use, especially in adolescent girls. The new OCP containing drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 0.03 mg (**together, termed as DEE**), is a combined oral contraceptive (COC) for the prevention of pregnancy in women of reproductive age, which acts by suppression of gonadotropins.



Structural formulae of EE and DRSP

Pharmacodynamics^{1, 2, 3, 4}

Oestrogenic Activity

Oestrogen acts synergistically with drospirenone in suppressing the cyclic pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH); in addition, oestrogen maintains the endometrium and helps to prevent breakthrough bleeding. The EE-induced increase in the levels of the sex-hormone-binding globulin (SHBG; 3- to 4-fold) and corticosteroid-binding globulin (CBG; 2- to 2.5-fold) were not affected when women were given DEE.

Progestogenic Activity

DRSP inhibits follicular stimulation and ovulation by suppressing LH. It also helps to prevent fertilization by changing the cervical mucus, thereby slowing sperm transport and affects ovum implantation through atrophy of the endometrium during treatment. DRSP inhibits ovulation in a dose-dependent manner; the optimal oral dosage is 3 mg.

Antimineralocorticoid Activity

In a normal menstrual cycle, urinary sodium and aldosterone excretion, and PRA (plasma

renin activity) and plasma aldosterone levels are significantly higher in the luteal phase of the cycle than in the follicular phase. This physiological natriuresis is due to the antimineralocorticoid activity of progesterone.

Like endogenous progesterone, DRSP has an antimineralocorticoid effect on the renin-angiotensin-aldosterone system. It causes natriuresis when given as a single agent or in combination with EE. No significant changes were observed in serum sodium, creatinine, or potassium levels when women were given DEE (DRSP 3 mg/EE 15–30 mcg), or EE 30 mcg/LNG 150 mcg.

Antiandrogenic Activity

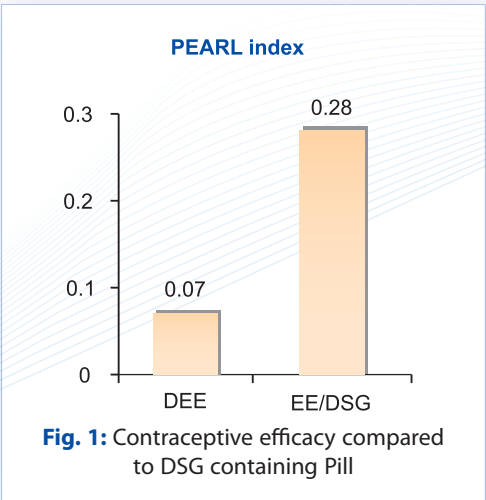
DRSP, Cyproterone acetate and dienogest are the only progestogens demonstrating antiandrogenic activity at therapeutic dosages. Anti-androgenic activity occurs due to competitive androgen receptor-binding. DEE directly reduces the production of testosterone and its precursors by inhibition of steroidogenic enzymatic activities, resulting in a decrease in seborrhoea, acne, and hirsutism in women.

Clinical Efficacy^{1,5,6}

Contraception

The efficacy of DEE as an OC has been assessed in over 31,000 monthly cycles in more than 2,400 healthy women of reproductive age. When used correctly, the efficacy of OCs is greater than 99%; however, typical rates of efficacy range between 92% and 97%, indicating that non-compliance is the main reason for “failure” of OCs.

Studies comparing DEE with an established OC (EE/DSG) reported relative contraceptive efficacy by using a comparison of Pearl index outcomes. The oral DEE combination was highly effective in preventing pregnancy in young healthy women who required contraceptive protection. Pregnancy rates of 0.3–0.7% with corrected Pearl indices (i.e., those derived from data excluding cycles where condoms were used) of 0.41–0.71 were recorded in clinical trials of DEE for 13 and 26 monthly cycles in 326–1,657 women (total, 3,192 women with 18,418 cycles).



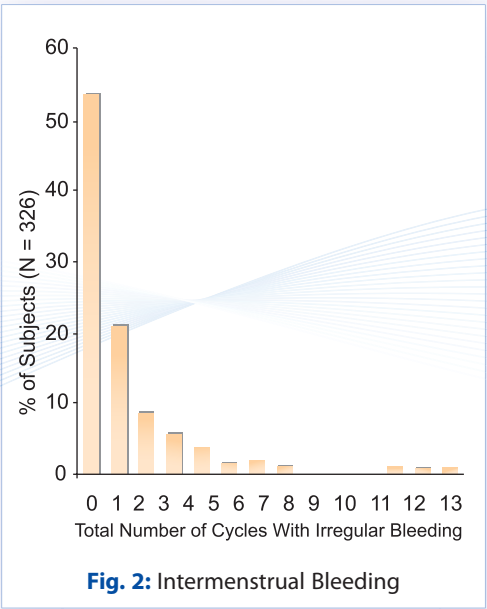
The Pearl index, taking only the method failure into consideration, is 0.07 for DEE. One pregnancy due to a method failure

occurred during the use of EE/DSG; the resulting Pearl index was 0.28.

Cycle Control^{1, 6, 7}

Cycle control (measured by the incidence of intermenstrual bleeding) in women receiving DEE appears to be good, with a low incidence of intermenstrual bleeding after the first cycle, which is maintained for up to 26 cycles.

In three clinical trials, the incidence of intermenstrual bleeding was greatest in the first cycle, and decreased over the study period. As with other OCs, spotting may occur more often in women using DEE for the first time than in those switching from another OC. About half of the women using DEE reported no intermenstrual bleeding.



Premenstrual Symptoms^{7, 8}

The impact of the new progestogen, DRSP, on self-perception women have regarding their menstrual health has been evaluated in many studies. Treatment with DEE improves subjective feelings of well-being

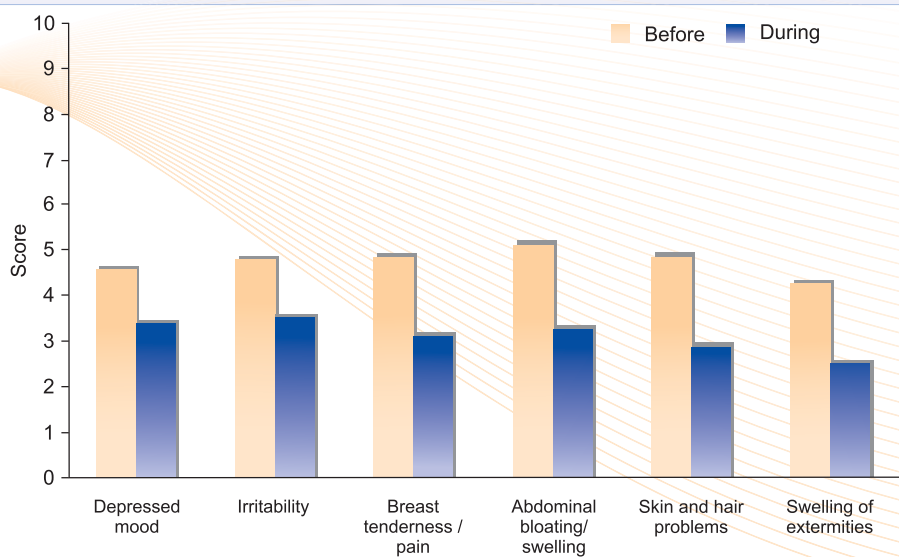


Fig. 3: Mean changes in menstrual related symptoms from baseline to cycle 6 for three phases of the menstrual cycle.

in women. Women have reported that symptoms of water retention, negative affect, and increased appetite significantly improved after treatment.

Only approximately 4% of respondents stated that they did not suffer from any symptoms in the days preceding their menses. Overall, depressed mood, irritability, breast tenderness or pain, abdominal bloating or swelling, or skin and hair problems were reported by 52–66% of the respondents prior to initiating treatment. The greatest improvements occurred for skin and hair problems, abdominal bloating or swelling, breast tenderness or pain, and swelling of the extremities.

Statistically significant decreases from baseline to cycle 6 were observed for all subjects and in all menstrual phases for negative affect and water retention. The low rate of discontinuation of DEE could result, in part, from the positive effect it had on perceptions of water retention and negative affect.

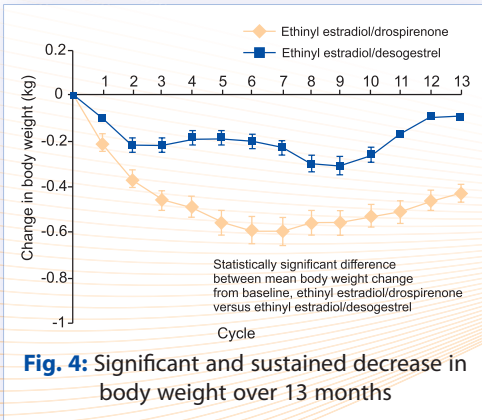
Antimineralocorticoid Activity^{1,6,9,10,11}

Progesterone has a high affinity to the mineralocorticoid receptor, for which it is an antagonist. Almost all synthetic progestogens are devoid of this antimineralocorticoid effect. They are unable to antagonize the salt-retaining effect of oestrogens. This could be one cause of the weight gain and increase in blood pressure that is seen with the use of COCs and, in some susceptible women, with postmenopausal oestrogen/(progestogen) treatment. A frequent finding in COC users is the occurrence of various degrees of oedema and other symptoms related to fluid retention, which cause poor compliance. This was reversed in OC with DRSP and hence had better patient compliance.

Body Weight^{1,6,7,8}

DEE appears to cause little change in mean body weight during treatment. Most women who took DEE for up to 26 cycles either maintained their baseline body

weight or experienced a small body weight loss over the majority of cycles.



Antiandrogenic Benefits

Seborrhoea and Acne^{1, 8}

COCs are a highly effective treatment option for acne in women, particularly in those with symptoms of hyperandrogenism. The beneficial effects of COCs on acne are partly due to their ability to reduce androgen secretion by the ovaries and to increase the levels of the SHBG. Moreover, some progestins, such as DRSP, CPA, and dienogest, have marked antiandrogenic activity, thereby partially counteracting the effects of endogenous androgens. Furthermore, DRSP has antiandrogenic properties through direct actions at the androgen receptor site, which, when combined with EE in an OC, make it a suitable option in the treatment of acne and other skin-related conditions, in addition to other hyperandrogenic disorders such as hirsutism.

In a survey conducted in 10,947 users of DEE, 74% reported that their skin condition had improved since they started treatment. Moreover, 90% of the respondents were satisfied or very satisfied with the current appearance of their skin while receiving this

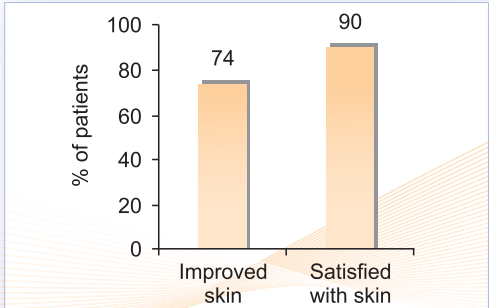


Fig. 5: Improved skin

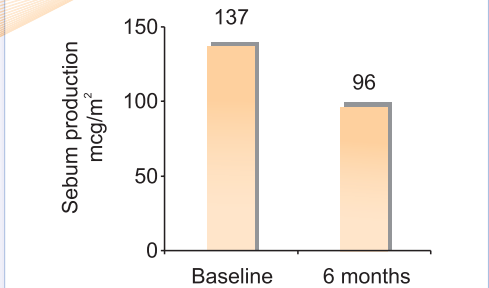


Fig. 6: Decreased sebum production

COC. In other studies, DEE reduced sebum production and hair growth on the upper lip and chin, as well as increased SHBG levels and decreased androgen levels.

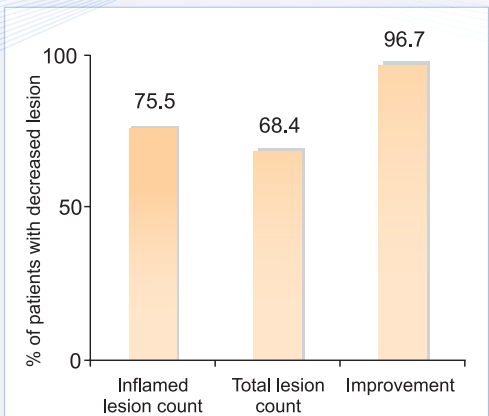


Fig. 7: Decrease in acne lesions

Hirsutism^{1,8,9,11}

COCs containing CPA and DRSP have been proved effective for the treatment of acne and facial hirsutism. Their progestational activity lowers LH secretion and, hence, the release of LH-mediated ovarian androgen. DRSP has antimineralocorticoid and antiandrogenic activity and its pharmacological and biochemical profiles are similar to those of endogenous progesterone. Its important feature is that it does not attenuate the EE-induced increase in the SHBG; neither does it interfere with androgen binding to the SHBG.

Hirsutism is assessed at 6-month intervals using the Ferriman-Gallwey (F-G) scoring system.

There is a statistically significant decrease in the total hirsutism score, as well as a

significant decrease in hair growth on all body parts after 6 and 12 months of therapy, when compared with baseline values. After 6 months, diminished hair growth is more evident on the chest, waist, thighs, and arms.

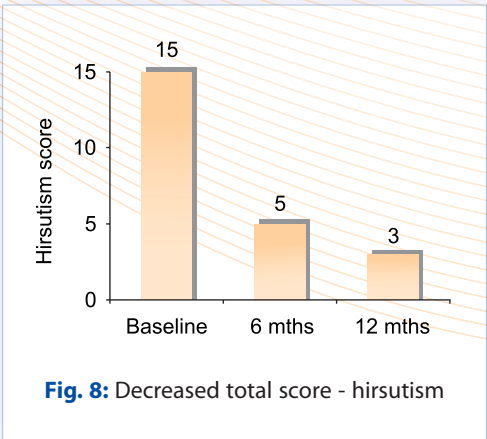


Fig. 8: Decreased total score - hirsutism

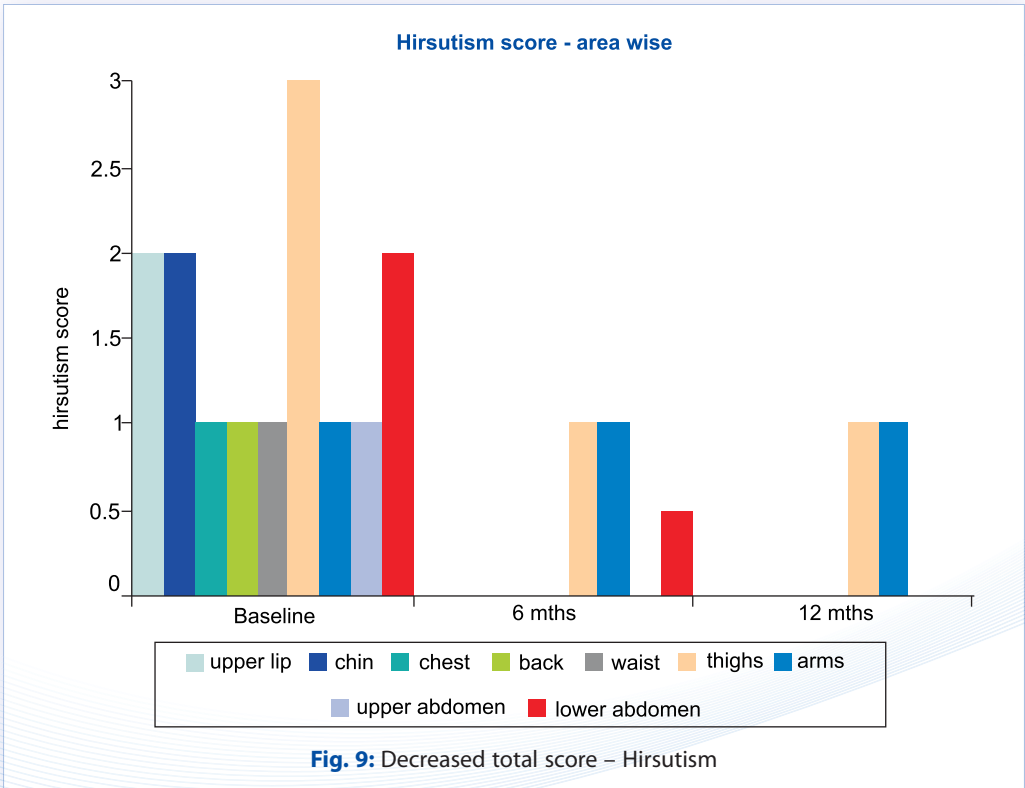


Fig. 9: Decreased total score – Hirsutism

Hyperandrogenism itself, as well as progestins with androgenic activity, counteracts the beneficial effect of oestrogen on serum SHBG concentration. Thus, treating hirsute patients with COCs containing high doses of oestrogen together with progestins devoid of androgenic activity (i.e., CPA or DRSP) has much less effect on the SHBG concentration and they should, therefore, be more effective for the treatment of hirsutism.

Safety Profile^{1,5,7,8,10}

For women who require ongoing contraception, poor tolerability is the most frequent reason to discontinue OCs.

DEE and Carbohydrate Metabolism¹¹

DEE did not cause any major changes in the fasting blood levels of the carbohydrate variables, even during long-term use. There was no shift towards an impaired glucose tolerance.

DEE and Lipid Profile¹⁰

There was a favourable change seen in the lipid profile, as there was an increase in mean HDL cholesterol with stable mean LDL cholesterol levels. This increased HDL/LDL ratio was clinically beneficial with respect to cardiovascular disease risk. Mean triglycerides levels increased, but were within the normal range.

DEE and Venous Thromboembolism (VTE)⁹

The 3-year interim results from a large, controlled, prospective postmarketing surveillance study suggest a VTE rate of:

- 61/100,000 women-years for DEE, *which is similar to the rates of*
- 60/100,000 women-years for LNG-containing OCs

DEE does not increase the rate of thromboembolic events compared with other OCs

Hyperkalaemia¹¹

DRSP is an analogue of spironolactone. Consequently, there is a theoretical potential for hyperkalaemia to develop in some women who take an oral formulation containing DRSP, particularly when DRSP-containing formulations are co-administered with potassium-sparing agents in women with severe renal impairment.

No cases of hyperkalaemia in women on DEE were detected, compared to 15/100,000 women-years in other OC groups. There were fewer reports of events related to hyperkalaemia (electrolyte disturbances, syncope) with DEE versus other OCs (U.S. Phase IV Study).

Pill Usage

Indication

For the prevention of pregnancy in women who elect to use an oral contraceptive. The pack consists of 21 tablets of a monophasic combined hormonal preparation, followed by a 7 day pill free period. It is recommended that **the pill** be taken at the same time each day, preferably after the evening meal or at bedtime.

The estrogen related side-effects and risks are the same as for all other COC. For details see chapter 14 and 15.

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated via *in vitro* and *in vivo* studies. The potential effect of

DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetics study, using omeprazole as a marker substrate. Based on the available results of *in vivo* and *in vitro* studies, it can be concluded that, at a clinical dose level, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

Interactions with Drugs that have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking the **pill with DRSP** with other drugs. Of note, occasional or chronic use of NSAID medication was not restricted in any of the clinical trials.

Contraindications for DRSP containing pill is contraindicated in patients with

- Renal insufficiency
- Hepatic Impairment
- Pregnancy
- Lactation
- Paediatric Use

Conclusion

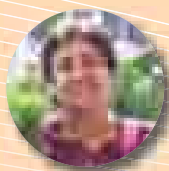
It is evident that DEE is an effective contraceptive with an excellent Pearl Index. Available data indicate that DEE is a SAFE OC, with no effect on the impairment of carbohydrate and lipid metabolism, no increased risk of VTE, and results in effective suppression of endometrial activity. Additionally, it has benefit in hyperandrogenic state because of its anti-mineralocorticoid effect. It is a welcome addition to the basket of choices towards decreasing the unmet need for contraception.

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Chapter 8

Myths and Facts on OC Pills



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“The great enemy of truth is very often not the lie – deliberate, contrived and dishonest but the myth – persistent, persuasive and unrealistic.”

John F Kennedy

Way back in the late fifties oral contraceptive pills came into existence. The pill underwent tremendous modifications over a period of years. However a lot of misconceptions about the pill still haunt the minds of the end-users as well as the medical professionals prescribing them. This may be attributed to the following two factors:

- The average Indian lady considers her neighbors/friends as her close confidantes and advice regarding contraception comes from these sources rather than qualified medical professionals.
- These ladies still consider the OC pills unsafe and are not aware of the newer developments.

The reason for discontinuation or dissatisfaction is not the major side effects of the pills but the minor and temporary problems like nausea, vomiting and weight gain. Proper counseling and education can solve these discomforts easily. The Indian lady usually starts the pills with a prejudiced mind expecting the so-called ill effects of the pills.

The following myths are commonly prevalent amongst the ladies, which should be cleared up before offering the pills as a method of contraception.

Myth: OC pills cause weight gain

FACT: Not all women experience weight gain. The minor increase in weight depends on the type of pill used and the woman's lifestyle. The weight gain is due to premenstrual fluid retention, which is a temporary phenomenon. This usually subsides gradually as the physiology gets adjusted to the altered hormonal milieu. Actual weight gain may be due to fertility control itself, which allows them better food, rest and tension free conjugal life. Weight fluctuations are very common during the reproductive years and are wrongly attributed to OC pills.

In fact newer pills with desogestral and cyproterone help in restricting weight gain due to their lower androgenic effects.

Pills with Drospirenone actually cause weight loss by helping in excretion of excess body water due to their mild diuretic action.

Myth: Pills users suffer from prolonged nausea and vomiting

FACT: Some ladies experience variable amounts of nausea and vomiting, however

this is a temporary effect, which passes off after a continued use of 2-3 months. Taking the pills at bedtime or with meals can easily reduce this initial hurdle. If required, anti-emetics can be prescribed. The newer third generation pills have lesser GI disturbances and nausea and vomiting are markedly reduced.

Myth: Women above the age of 35 years are unsuitable for OC pills

FACT: Women without high risk factors for hypertension, heart disease and stroke can safely take the low dose pills till menopause. In fact these pills are useful in tackling the problems of irregular or heavy periods in the perimenopausal age group. However OC pills are not recommended in smokers since the combination of estrogens and smoking can increase the risk of stroke.

Myth: Pills reduce the amount of breast milk in lactating mothers and may also affect the baby

FACT: Though this was true with the previous generation of pills, the newer generation 'progesterone only pill' has no effect on the quantity or quality of milk. These do not affect the growth of the baby.

Myth: Pills cause various malignancies

FACT: This is mired in controversy. However research work is still on to study the relationship. The pill significantly reduces risk of some cancers but has a doubtful role in increasing some cancers. There is conclusive data to prove that OC pills reduce the risk of ovarian cancer by 40% and endometrial carcinoma by 50% (IMAP 2002). The effect persists for 10 and 15 years respectively for the above-mentioned

diseases after 1 year of use. This should be emphasized while counseling.

Regarding breast cancer, WHO collaborative group in 1996 stated that young women using OC pills do not have an appreciably increased risk of breast cancer. Even this increased risk disappears completely 10 years after discontinuing the pill. In pill users developing breast carcinoma, the disease is localized and has better prognosis. All observations argue strongly against the pill causing development of new breast cancers (IMAP 2002).

Many large population based cohort studies (Walnut Creek) did not find any increase in the risk of carcinoma of the cervix in OC pill users. In a few studies where they found small increase in risk, it was not clear whether it is solely attributable to OC pills or to other associated factors like HPV infections, parity, sexual partners etc. (Guillebaud 1999, Dyer 2002).

According to WHO it is entirely acceptable to continue OC pills while monitoring or treating CIN. (WHO 2002).

The bottom line is OC pill users should have regular Pap smear, pelvic and breast examination.

Myth: OC pills cause myocardial infarction, stroke and thrombosis.

FACT: WHO study found no increased risk of heart attack amongst the healthy pill users. Two factors causing arterial thrombosis (myocardial infarction, stroke) and venous thrombosis (DVT, pulmonary embolism) are:

1. Amount of estrogen in the pill
2. Other associated high risk factors.

The newer pills with small amount of estrogen are safer. Other risk factors like

obesity, hypertension, family history and specially smoking have a greater impact. Thus low dose OC pills (less than 50 micrograms of ethinyl-estradiol) do not increase the risk of myocardial infarction or stroke in a healthy non-smoking woman regardless of age.

Myth: OC pills cause future infertility and birth defects

FACT: Usually there is no problem regaining fertility. Most of the ladies can conceive within three months of stopping OC pills. Pills do not cause abortions or birth defects. If given accidentally during early pregnancy, there is no risk of congenital anomalies in the developing fetus.

Myth: OC pills affect the sexual relationship

FACT: The pill has no effect on the sexual drive. On the contrary, there is no fear of pregnancy and hence the woman can enjoy sexual intercourse in a relaxed and tension free manner.

Myth: Pills prevent HIV infection

FACT: The pills do not prevent HIV infection but can be considered a safe contraceptive for HIV positive women.

Myth: OC pills are useful only as a contraceptive method and have no other benefits

FACT: The pills have many other non-contraceptive benefits like:

1. Regular periods
2. No dysmenorrhoea or menstrual irregularities.

3. Protection from benign breast diseases like fibroadenosis and fibrocystic disease.
4. No functional ovarian cysts.
5. Protection against anemia.
6. No premenstrual syndrome.
7. Protection against carcinoma of the ovary and endometrium.
8. Newer pills also protect against acne and hirsutism.

After knowing the facts if the risk/benefit assessment is performed, the benefits far outweigh the risks. In developing countries like India, where risk of mortality due to unplanned pregnancies, anemia and malnutrition is very high, proper education and counseling will go a long way in dispelling these myths. Hence it becomes the responsibility of the health care provider/ gynecologist to present these pills in the proper perspective.

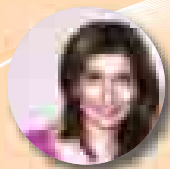
“The OC pill has changed but unfortunately the mind set has not.”

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Chapter 9

Missed a pill what next ?



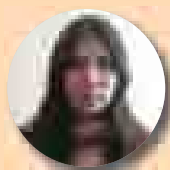
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Oral contraceptive pills are amongst the most common methods of contraception used these days. Equally common is missing these pills or irregular pill intake. Globally, it was estimated that in 2001 more than 2 million women became unintentionally pregnant due to improper use of oral contraceptives. Much of this improper use can be attributed to forgetting to take the pill on a regular basis. In a study conducted by Potter et al, in which an electronic monitoring device was used to measure the compliance of pill taking, it was apparent that consistency of pill taking is even worse than what is reported by the patients. In this study only one third (i.e. 33%) of women were documented to have missed no pills in the first month of use and by the third month, about one third of women missed 3 or more pills with many episodes of consecutive days of missing pills.¹ This indicates that women become less careful with time, emphasising the importance of repeatedly reviewing with them what to do when pills are missed. The instructions for what to do when pills are missed are complex, as instructions vary for different quantities of pills missed and for the particular week of the cycle in which the pills were missed. Indeed, research conducted in Jamaica suggests that pill clients often

provide incorrect responses for what action to take when one unintentionally misses oral contraceptive pills.²

To ensure regular pill taking and to avoid missing pills, the pill should be keyed to a daily event like with dinner or at bed time. Missing a pill can impair the contraceptive efficacy plus can lead to symptoms like irregular spotting or bleeding. The following advice is usually given in case of missed pills:

If 1 pill is missed by the woman, she should take that pill as soon as she remembers and take the next pill as usual, no backup is required.

If she misses two pills in the first two weeks, she should take two pills on each of the next two days. Though it is unlikely that a backup method is required, it is better to recommend a backup method for 7 days.

If two pills are missed in the third week; or if more than two pills are missed any time, another form of contraceptive should be used as backup immediately and for the coming 7 days, and a new pack of pills should be started.

In case of gastrointestinal upset (vomiting or diarrhoea), women are instructed to use backup for at least 7 days even if no pills

have been missed, as these conditions can lead to altered absorption.

Whether missing a pill has any impact on contraceptive efficacy or not is another issue. Letterie et al demonstrated that skipping four consecutive pills at varying times in the cycle did not result in ovulation.³ Even women who deliberately increased their pill-free interval to 11 days did not show any signs of ovulation.⁴ Similar results have been observed with the lowest dose COC's.⁵ These studies are however limited by the small number of women studied. As there are large individual variations, it is possible that some women might be at risk of ovulation with a small increase of the pill free interval. However even in these women progestational effects on cervical mucus and endometrium ensure a good contraceptive efficacy.⁶ Although these studies may well prove that a women's chance of getting pregnant with missing pills is nearly zero,

the conventional advice followed is still the safest message to convey.

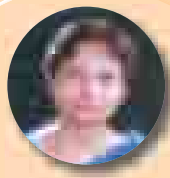
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Chapter 10

Oral Contraceptives – More than just a contraceptive



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The oral contraceptive (OC), commonly known as the “PILL” is the widely accepted and most effective method of fertility control. Currently more than 100 million women rely on the pill. In developing countries 14% of married women of reproductive age use pills while in developed countries about 6% of women in reproductive age use pills for contraception.¹

Its use would have been more widespread, particularly in developing countries, but for fear about the alleged health risk which were publicized in 1960's and 1970's. Recent review by the cohort, as well as other studies find OC risk lower than expected, and the benefit greater.

Here we focus on other health benefits of OC beside providing a very effective,

convenient and safe contraceptive method. Large scale cohort and case control studies in the last 10 – 15 years, have produced striking evidence of important non-contraceptive benefits of OC's.²

The public remains largely unaware of such benefits. Even in US, 61% of women surveyed had little knowledge about non-contraceptive benefit of the pills. These benefits of OCs can be categorized as:

- A) Fertility related benefit
- B) Menstrual benefit
- C) Prevention of benign gynecological disease
- D) Prevention of malignant gynecological disease
- E) Other emerging benefits (Box I)

BOX I: Non Contraceptive Benefits of Oral Contraception

Established Benefit:

- A. Menstrual benefit – (i) Regular menstrual cycle, (ii) Reduced blood loss, (iii) Reduced iron deficiency anemia, (iv) Reduced dysmenorrhoea
- B. Inhibition of Ovulation – (i) Fewer ectopic pregnancies, (ii) Fewer trophoblastic diseases, (iii) Fewer ovarian cysts
- C. Other benefits – (i) Reduced fibroadenoma/ Fibrocystic breast disease, (ii) Reduced acute pelvic inflammatory disease, (iii) Reduced endometrial cancer, (iv) Reduced ovarian cancer
- D. Emerging Benefit – (i) Increased bone mass, (ii) Reduced acne, (iii) Reduced colorectal cancer, (iv) Reduced uterine leiomyomata, (v) Reduced rheumatoid arthritis (vi) Treatment of bleeding disorders, (vii) Treatment of hyper androgenic anovulation, (viii) Treatment of endometriosis, (ix) Treatment of perimenopausal changes

From Burkmen R et al, Am. J. Obst. Gynecol 2004

A) Fertility Related Benefits

Oral contraceptives prevent unwanted pregnancy very effectively. All types of pills – combined estrogen–progestin (including multiphasic) and progestin only – are effective and thus it reduces maternal morbidity and mortality related to pregnancy complications.^{2,3}

Beside reducing unplanned and high risk pregnancy rates, OC's have following fertility related benefits–

a. Ectopic Pregnancy – Ectopic pregnancy is a life threatening condition and cause of secondary infertility. Since all types of OC's are highly effective methods of preventing ovulation, protection against ectopic pregnancy is an important benefit for all women who take the pills.³

b. Trophoblastic Disease – Because OCs prevent ovulation, they presumably protect against trophoblastic disease, including molar pregnancy and choriocarcinoma, which are potentially life threatening diseases involving abnormal cellular growth developing from the fertilized ovum.

c. Pelvic Inflammatory Disease – Women who use OC's face about half the risk of developing PID than non users. OC's reduce the risk of PID by thickening the cervical mucus, thus hindering the ascent of pelvic infection. Thus long term use of OC's reduces the PID related morbidity, and infertility, and economic burden related to its treatment.^{3,4}

B) Menstrual Benefits

a. Menorrhagia & Dysfunctional Uterine Bleeding – OC generally improves menstrual pattern. Bleeding is less, cycles are regular

and predictable, and overall menstrual bleeding is less painful. Nowadays low OC pills contain fairly low levels of estrogen, thus there is less build up of uterine lining each month. So menstrual bleeding is sometimes shorter and lighter.⁵

b. Dysmenorrhoea – OC's are highly effective in relieving dysmenorrhoea by inhibiting P.G. production. Combined OC's are more effective in relieving dysmenorrhoea than the progestin only pill.^{5,6}

c. Makes Menopause Easier – The contraceptive pills are also said to soothe mood swings, insomnia and hot flushes – associated with menopause.

d. Pre-menstrual Syndrome and Mittel Schmerz – Symptoms of pre-menstrual syndrome are less in users of OC's. OC's also block the surge of hormone before ovulation and are effective for relieving mid cycle pain or spotty bleeding.

e. Iron Deficiency Anemia – In developing countries anemia is a serious health problem among women because of inadequate diet, parasitic infections, repeated pregnancies etc. In OC users women may lose one third to one half the blood iron lost as compared to non OC users. Thus OC users are less liable to develop iron deficiency anemia and confer great advantage in reducing anemia related maternal and child morbidity and mortality and treatment cost.^{6,7}

C) Protection against Benign Disease

a. Benign Breast Disease – OC users lower the risk of fibroadenoma and fibrocystic breast disease by 50–75%. Protection against

benign breast disease increases proportionally with length of pill use and progestin content of pill. Since most OC's now in use contain lower amount of progestin, they may offer less protection against benign breast disease.⁶

- b. Functional Ovarian Cyst** – OC use protects women from functional ovarian cyst. The risk of follicular cyst goes low by 50% and that of corpus luteal cyst by about 80%.¹ As these functional cysts depend upon ovulation, the benefits applies only to current pill users. Low dose OC's and multiphasic OC's, provide less protection against cysts as though they effectively prevent ovulation, they may permit some follicular development.
- c. Fibromyoma of the Uterus** – A long term study by the Oxford Family Planning Association has shown that the risk of uterine fibroid is reduced by about 30% in women who have used OC for 10 years, and that the lowered risk is proportionate to length of use. While there is no clear consensus as yet, the evidence does seem to show that low dose OC's help reduce fibroids.^{1,8}
- d. Endometriosis** – Combined OC's control endometriosis to a good extent. Low dose pills may also be tried to begin treatment, to be switched over to high dose pill later on.

D) Protection against Malignancies

OC's help to protect women from two cancers of reproductive organs – (i) Endometrial cancer, (ii) Epithelial Ovarian cancer. Studies suggest that these cancers are about half as common among OC users as compared to non OC users.

- a. Endometrial Cancer** – Even as little as one year of use of combined OC's cut the risk of endometrial cancer substantially and protection lasts long after women stop using OC. Longer use of OC significantly increased protection. Progestin component in the pill is thought to counteract the effect of estrogen, which would otherwise encourage cell division.⁹
- b. Epithelial Ovarian Cancer** – Combined OC's help to protect against epithelial ovarian cancer by reducing gonadotrophin production by the pituitary gland, thus reducing the effects of gonadotrophin stimulation of the surface cells of ovaries. The large 1985 CASH study and many smaller studies have confirmed the preventive role of OC's against epithelial ovarian cancer.¹⁰ It is by far the most common type of ovarian cancer especially in the age group above 60. The protective effect of OC's against it may grow in importance in the coming years, as widespread OC use may eventually result in a decline in the incidence of this frequently fatal disease.
- c. Colorectal cancer** – Some studies have found that women who had ever used OC's reduced their risk of colorectal cancer to 60% of that of non-users and that OC used for over two years reduced risk to 50%.¹¹ Colorectal cancer is the fifth most common cancer among women world-wide. However it requires further long term case control studies to confirm the protective effect of OC's on colorectal cancer.

E) Other Possible Health Benefit

- a. Acne and Hirsutism** – Low dose OC pills, triphasic pills

are effective in treating hyper androgenic conditions like acne and hirsutism over time (a year or more) by decreasing sex hormone binding globulin and significantly decreasing free testosterone level.¹² Newer OC preparations with Cyproterone and Drospirenone are more effective in this respect.

b. Bone Density – Some studies suggest that OC use may stabilize or even increase bone density. Evidence suggests that bone mass benefit of OC may be related to the estrogen dose. So some very low dose pill may not help prevent loss of bone density. Though till now neither of studies has demonstrated that the effects of OC on bone density makes a practical difference or protects postmenopausal women from bone fracture.¹²

c. Rheumatoid Arthritis – A large study analysis concluded that OC's have a protective rather than preventive effect in the development of rheumatoid arthritis and may reduce progression from the mild to severe stage of the disease.

Concluding Remarks

Other health benefits of OC's apart from providing very effective, simple, aesthetic, reversible means of contraception should be highlighted whenever couples or women are to be counseled for OC's. It is to be noted that about 25% of women who try the pill, give it up because of myths and fears. These wrong old ideas about the harmful effect of OC's not only are still haunting the minds of Indian people but also the medical professionals and para medicals.

Dissemination of knowledge about the relative vast benefit of OC's is essential. It is

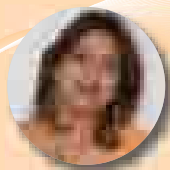
possible through training of family welfare workers and mass media education, which should highlight so many other benefits of OC's like prevention of menstrual symptoms, nutritional and cosmetic benefit and above all prevention of benign and malignant disease of breast, uterus and ovaries.

The Government of India is now promoting more actively the use of OC's in Maternal Family Welfare Program. It is essential that in popularizing the use of different types of pill combination, the approach should be positive which should start from other benefits rather than side or adverse effect of OC's.

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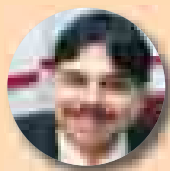
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Oral Contraceptives and IVF



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Oral contraceptive pill pretreatment is widely applied in women undergoing ovarian stimulation and GnRh antagonist and GnRh- α . It is not only useful in scheduling cycles, but also has multiple benefits. In this chapter we shall learn about its effect on the endocrinology and the pregnancy rates.

Effects of oral contraceptives administered at defined stages of ovarian follicular development

Ovarian follicular dynamics are complex phenomena comprising of a series of morphologic and physiologic events. Two or three waves of follicular development occur during the human menstrual cycle. Major waves are those in which a dominant follicle is physiologically selected for preferential growth over subordinate follicles, and minor waves are those in which selection does not occur. Major ovulatory waves and major anovulatory waves have been detected. Physiologic selection in major waves occurs within the first 3 days after wave emergence at a diameter of approximately 10mm. The preferential growth of the dominant follicle

and regression of subordinate follicles in major waves is believed to occur in association with decreasing FSH levels, and increased production of E2 and inhibition from the granulosa cells.

Information about follicular development and atresia during spontaneous menstrual cycles provides insight into the mechanisms underlying follicular development during the use of oral contraceptives (OC). Ovarian follicular development is not completely suppressed during OC use. Ovulatory and anovulatory follicles have been reported in women taking OC and endogenous E2 levels reportedly attain preovulatory levels. The incidence of follicular activity during OC use depends on the type and dose of steroid hormones used in the formulation. There is increasing evidence to suggest that the degree of pituitary-ovarian suppression is related to the dose of estrogen (E), whereas the type and dose of progestin are less important.

The incidence of follicle growth during OC use also depends on the administration scheme used. Starting OC on the first day of menses has been shown to effectively suppress follicular growth. In contrast, women who use the "Sunday Start"

regimen, in which the first OC dose is taken on the first Sunday after menses begins, may be at a greater risk of developing follicles capable of ovulating. Follicle development during OC use is associated with a loss of gonadotropin suppression during the hormone – free interval. Follicle development and endogenous FSH levels during the hormone-free interval have been reported to reach levels comparable to those observed during the early follicular phase of the natural menstrual cycle. Resumption of OC at the end of the hormone-free interval resulted in decreased FSH, despite continued growth of dominant follicles.

Various uses are:

- Scheduling cycles for batch IVF
- Selecting a synchronized cohort of follicles
- For patients at high risk to OHSS undergoing COH
- Poor responders
- Avoid cyst formation after agonist administration
- To reduce high levels of LH prior to controlled ovarian hyperstimulation

1) Scheduling cycles for the batch IVF:

Cycle programming is an integral part of the work of an IVF centre especially in our country. Usually the embryologists are free lancing and are working with different centres. Also it is economical to perform batch IVF in centres where the number of patients are less, the media and disposables can be utilized optimally. It also allows a method to schedule a more consistent and reliable workload for the IVF staff.

Oral contraceptive pill (OCP) pretreatment has been used in *in vitro* fertilization since the pre-analogue era to assist

in cycle programming and to avoid a premature LH surge.¹ The gold standard to avoid premature LH surge is down regulation with GnRH agonists. After the recent introduction of GnRH antagonists in ovarian stimulation, OCP has been used for cycle scheduling purposes. Cycle programming has become more difficult with the use of GnRH antagonists, as stimulation initiation is dependent on the occurrence of menstruation. Several studies using GnRH antagonists for inhibition of premature LH surge have been performed using OCP pretreatment to assist in cycle scheduling.² Pretreatment with OCP compared with initiation of stimulation on day 2 of the cycle in patients treated with GnRH antagonist and rFSH appears to be associated with a not significant difference in ongoing pregnancy rates per started cycle and results in a significantly higher early pregnancy loss after a longer stimulation period and an increase dose of FSH.³

Cetrorelix pretreated with OCPs resulted in similar number of oocytes retrieved compared with a long buserelin protocol. Both regimens were well tolerated and allowed scheduling of the oocytes retrieval, with only a small number of retrievals falling on a weekend or public holiday.⁴

The OC pretreatment in recombinant FSH/GnRH – antagonist protocols provides a patient-friendly regimen and can be optimized for weekday retrievals. No difference was seen in the number of 2PN embryos, cryopreserved embryos, embryos transferred, implantation and pregnancy rates between the two stimulation protocols.⁵

Nevertheless, planning treatment cycles may be more difficult with

GnRH antagonists. Ovarian stimulation treatment should start on day 2 or 3 of menses. IVF clinic centres that avoid oocyte retrievals and embryo transfers during weekends prefer to start gonadotropin treatment at previously planned dates, rather than on day 2 or 3, facilitating scheduling of fertilization procedures.⁶

The three regimens produced similar numbers of oocytes and good quality embryos. However, the greater convenience of using OC for scheduling needed a slightly more rFSH dosage in observational studies.⁷

2) Selecting a synchronized cohort of follicles:

Effects of oral contraceptive, synthetic progestogen or natural estrogen pre-treatments on the hormonal profile and antral follicle cohort before GnRH antagonist protocol showed that a 5-day free interval after OCP or progestogen offers the advantages of gonadotropin recovery and homogeneous follicular cohort, whereas early FSH rebound occurring after estrogen pre-treatment argues for a short free period in these cases. Scheduling of antagonist cycles with 14-28 days of OC treatment had a marked impact on the hormone profiles and follicular development, although the final outcome in terms of the number of oocytes and good quality embryos was similar. The pituitary suppression due to OC use resulted in very low FSH and LH levels at the start of the cycle, even lower than those seen in along down-regulation group.⁸

3) For patients at high risk to OHSS undergoing COH.

Currently, one of the standard COH protocols, used for high risk patients undergoing IVF is the dual pituitary

suppression with oral contraceptive pills (OCPs) and GnRH agonist overlap followed by hCG to induce oocyte maturation. Despite its benefits, this protocol does not completely eliminate the development of OHSS, because the administration of hCG results in a prolonged luteotropic effect, which may result in a potential risk of OHSS in high-risk patients.

4) Poor responders:

OCP pretreatment has been used to improve the outcome in poor responders.⁹

5) Avoid cyst formation after agonist administration:

OCP pretreatment has been used to avoid cyst formation after agonist administration.¹⁰

6) To reduce high levels of LH prior to controlled ovarian hyperstimulation.

The addition of OC pretreatment to ganirelix cycles appeared to reduce the occurrence of LH rises, approaching the percentages obtained with a traditional GnRH agonist protocol (1.8 and 0.9% respectively). This can be attributed to the suppression of pituitary LH production by the OC prior to ovarian stimulation.

A longer gap between discontinuation of OC treatment and the start of other, smaller studies, which used a gap of 4-5 days, have produced more favourable pregnancy rates.^{1,11,12}

Drawbacks

Based on the current evidence, we consider that OCP pretreatment in GnRH antagonist protocols remains an effective option for cycle programming. The only possible drawback we would highlight is the higher

doses of gonadotrophins and the longer duration of ovarian stimulations required, which could have a negative impact in low responders and aged patients.^{1,3,11}

Conclusions

Oral contraceptive pre-treatment for ovarian stimulation in a GnRH agonist or a GnRH antagonist cycle has been recently investigated. Oral contraceptive scheduling of a GnRH agonist or a GnRH antagonist protocol results in follicular growth and hormone profile are similar to those observed in GnRH agonist protocols. The number of premature LH rises remains low. Similar numbers of oocytes and high quality embryos are obtained. This is significant because the use of the oral contraceptive pretreatment method significantly improves scheduling in a typical IVF program operating Monday to Friday. The greater convenience of oral contraceptive pretreatment scheduling appears to be off-set by the need for longer stimulation protocols and more FSH than with non-schedule regimen.

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Chapter 12

Contraceptive Vaginal Ring



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“No Woman is completely free unless she has control over her own reproductive destiny.”

Margaret Sanger

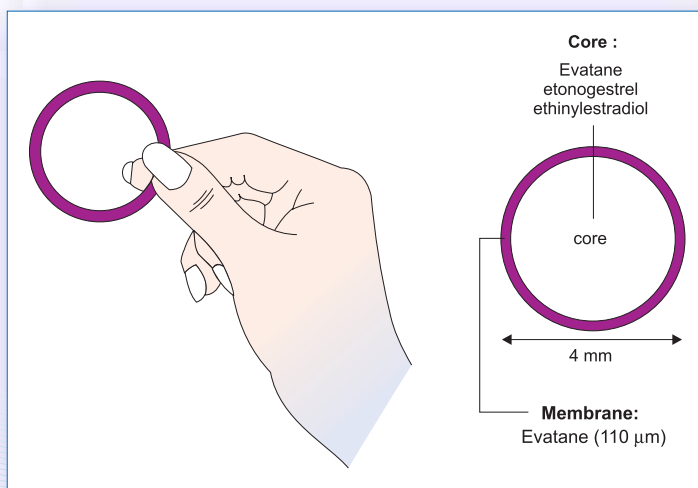
Introduction

India being a populous country still has a major unmet need for contraception and newer methods in the cafeteria menu should be made available to these vast numbers. Combined oral contraceptives are a popular choice for many women, with the disadvantages of daily administration, compliance and fluctuation of hormone levels and unacceptable cycle control at doses less than 20 mcg. Based on this scenario and to undo certain deficiencies

the vaginal contraceptive ring was developed.

This contraceptive vaginal ring (Nuva ring, Organon USA, Roseland NJ) is a flexible ring composed of Ethinyl Vinyl acetate (EVA) 54 mm in diameter and 4mm in cross section. It releases 15 mcg of Ethinylestradiol (EE) and 120 mcg of etonogestrel (ENG) per day.¹ Etonogestrel is 3-Keto desogestrel, a third generation progestin. The FDA approved the Nuva ring for contraceptive use in October 2001, though it is still not available in India.¹

Additionally, a progesterone only releasing ring is currently available in Peru and Chile for breast feeding women, and a 1 year ring releasing EE and Nestorone (a 19-nor



progesterone) derivative is now on trial in the U.S.

Usage

Each Nuva ring contains 2.7mg EE and 11.7 mg ENG uniformly dispersed within the EVA core. The ring is easily inserted and removed by the women at home. The ring acts for 21 days and is then removed for 7 days during which the woman has a scheduled bleed. The ring may be removed from the vagina for up to 3 hrs period without decrease in efficacy off label; the ring can be worn continuously for a 28 day cycle or a calendar month cycle.

Efficacy

In efficacy the vaginal ring equals the oral contraceptive. The European 1 year phase 3 study revealed that the ring is highly efficacious. There were 6 pregnancies out of 1145 women in the intent-to treat group, giving an efficacy rate of 99.5% and a pearl index of 0.65.²

Contraceptive efficacy of Nuva Ring

	Women following protocol (n=1049)	Overall (n=1146)
Treatment cycles	9880	12,109
Pregnancies	3	6
Overall Pearl Index	0.40	0.65
(95% CI)	(0.08–1.16)	(0.24–1.41)

Contraceptive efficacy of Nuva Ring (Roumen et al. 2001).

Mechanism of action

This ring completely inhibits ovulation³, as the primary mechanism of action. A reduction of ovarian estradiol secretion is observed and the lack of corpus luteum formation results in the absence of endogenous Progesterone. In addition,

the atrophic endometrial changes and thickened cervical mucus likely contribute to reduced fertility.

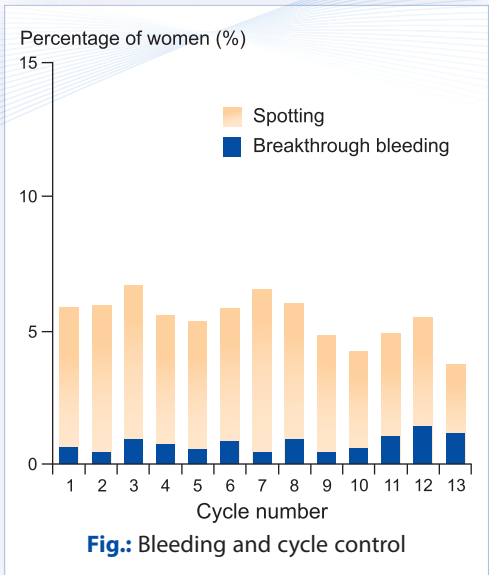
Acceptability

The contraceptive vaginal ring has been found to be highly acceptable to women, with 96% being satisfied and 97% reporting they would recommend the ring to a friend. The level of acceptability increases with duration of use. At baseline 66% of women found the ring to be acceptable, 81% after 3 months of use.

Bleeding and cycle control

This combined ring has been shown to have excellent cycle control with very few women having unscheduled bleeding. The incidence of irregular bleeding is 5.5% per cycle with majority of the bleeding being defined as spotting.

Virtually all women using Nuva ring experienced scheduled withdrawal bleeding (occurring in 98.5% of cycles).



Effects on the Vagina, Cervix, Endometrium and Metabolism

Several studies have shown that the Vaginal ring has no detrimental effects on the vaginal, cervical mucosa or the endometrial lining. An open-label study of 58 women with 13 cycles found no unfavorable effects of the ring on the cervical or vaginal mucosa.

Nuva ring has a minimal effect on carbohydrate metabolism. It has limited effects on the haemostatic variables, which are similar to those of a combined OCP.^{1,2,3}

Starting the Ring

Women who are not using another contraceptive method should insert the ring between 1-5 days of the cycle. If they start the method after day 5 of their cycle, they should use a back-up method for the first 7 days of the ring use. Conventionally patients are instructed to begin the ring on the first Sunday of the menses. However day 1 start is also both safe and effective. The ring may be inserted within 5 days of a pregnancy termination or miscarriage without increased risk of Infection.^{2,3}

Adverse Effects

In a large phase 3 trial, the most frequently reported events were vaginal complaints (vaginitis 13.7%, leukorrhoea 5.9%) and headaches (11.8%). There were no serious adverse events. Women should be counseled regarding the probability of expulsion. If the ring is expelled it should be rinsed in tepid water and reinserted within 3 hours. If the ring is out of the vagina for greater than 3 hours, a back up method should

be used for the next 7 days. The WHO has created evidence based criteria for medical eligibility for the Vaginal contraceptive ring usage based on various parameters.^{1,3}

Conclusion

NuvaRing

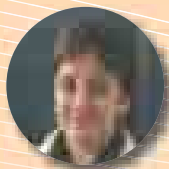
- is easy to insert and remove by the woman herself
- effectively inhibits ovarian function, resulting in good contraceptive efficacy
- is a robust method of contraception
- provides excellent cycle control despite the very low daily dose of ethinylestradiol; this is probably because of the uniform and sustained release of very low hormone doses from the ring
- has a neutral effect on body weight
- has a low incidence of adverse events such as breast tenderness, nausea and headache
- is associated with a high level of user and partner acceptability
- has no unfavorable effects on the vagina and cervix
- has minimal effects on various cardiovascular risk factors

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Chapter 13

Contraceptive Patch



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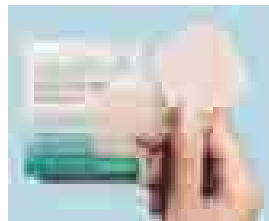
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***“Stop thinking in terms of limitations
and start thinking in terms of
possibilities.”***

Terry Josephson

Unintended pregnancies continue to be a major problem that affects not only the individual, but the larger society as well. These occur due to failure of contraceptive method or because the contraceptive method is difficult for the women to use consistently and correctly. Such a situation highlights the need for innovative contraceptive methods that are simpler to use, more efficacious, safer, and thus potentially result in increased user compliance.¹

While COC pills are a traditional way to deliver contraceptive hormones, a novel system for providing the same hormones (estrogen and progestin) was approved by the U.S. Food and Drug Administration in 2001. This system — a weekly transdermal contraceptive patch— has characteristics that may make it easier for women to use correctly and consistently. This may improve compliance, a problem among many COC users. The Trans-Dermal Contraceptive System or simply **THE PATCH**, is the first trans-dermal system of a combined contraceptive approved by the US-FDA. It is manufactured by ORTHO-McNEIL PHARMACEUTICAL INC., and is available by the name of ORTHO-EVRA.²



Description³

THE PATCH is a combination transdermal contraceptive patch with a contact surface area of 20 sq cm and measuring 4.5 sq cms. It contains 6.00 mg norelgestromin (NGMN) and 0.75 mg ethinyl estradiol (EE). It delivers continuous systemic doses of 150 µg norelgestromin (NGMN) and 20 µg ethinyl estradiol (EE) per day.

It is a thin, matrix-type transdermal contraceptive patch consisting of three layers.

1. **The backing layer** is composed of a beige flexible film. It provides structural support and protects the middle adhesive layer from the environment.
2. **The middle layer:** The active components in this layer are the hormones, norelgestromin and ethinyl estradiol.
3. **The third layer is the release liner**, which protects the adhesive layer during storage and is removed just prior to application.

Contraceptive Efficacy^{4,5}

- High Efficacy
 - Overall Pearl Index of 0.88
 - After 6 cycles, pregnancy possibility is half that of OC
- May be less efficacious in women ≥ 198 lb (90 kg)
 - NIH study in progress
- Compliance is superior when compared to OC
- Compliance unaffected by age

Pharmacodynamics

Norelgestromin is the active progestin largely responsible for the progestational activity that occurs in women following application of the Patch. For all Combination oral contraceptives the primary mechanism of action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Usage^{6,7,8}

The contraceptive patch is worn for one week, discarded, and replaced with a new one. A patch-free week follows three weeks of consecutive use.



This system uses a 28-day (four-week) cycle. A new patch is applied each week for three weeks (21 total days). Week Four is patch-free and withdrawal bleeding is expected during this time.

Every new patch should be applied on the same day of the week. This day is known as the "Patch Change Day." For example, if the first patch is applied on a Monday, all subsequent patches should be applied on a Monday. Only one patch should be worn at a time.

The patch should **not be cut, damaged or altered in any way**. If the patch is cut, damaged or altered in size, contraceptive efficacy may be impaired.

On the day after Week Four ends, a new four-week cycle is started by applying a new patch. **Under no circumstances should there be more than a seven-day patch-free interval between dosing cycles.**

If the patch becomes partially or completely detached and remains detached, insufficient drug delivery occurs.

If a patch is partially or completely detached:^{5,7}

For less than one day (up to 24 hours),	For more than one day (24 hours or more)
<ul style="list-style-type: none">• Reapply it to the same place or• Replace it with a new patch immediately.• No back-up contraception is needed.• The woman's "Patch Change Day" will remain the same.	<ul style="list-style-type: none">• SHE MAY NOT BE PROTECTED FROM PREGNANCY.• Stop the current contraceptive cycle and start a new cycle immediately by applying a new patch. There is now a new "Day 1" and a new "Patch Change Day."• Back-up contraception, such as condoms, spermicidal, or diaphragm, must be used for the first week of the new cycle

A patch should not be re-applied if it is no longer sticky, if it has become stuck to itself or another surface, if it has other material stuck to it or if it has previously become loose or fallen off. If a patch cannot be re-applied, a new patch should be applied immediately. Supplemental adhesives or wraps should not be used to hold the patch in place.

If the woman forgets to change her patch⁸

At the start of any patch cycle Week One /Day 1	In the middle of the patch cycle Week Two/ Day 8 or Week Three/Day 15		At the end of the patch cycle (Week Four/Day 22), Week Four (Day 22):
	For one or two days (up to 48 hours),	For more than two days (48 hours or more),	
Apply the first patch of her new cycle as soon as she remembers. There is now a new "Patch Change Day" and a new "Day 1." The woman must use back-up contraception, such as condoms, spermicide, or diaphragm, for the first week of the new cycle	She should apply a new patch immediately. The next patch should be applied on the usual "Patch Change Day." No back-up contraception is needed.	SHE MAY NOT BE PROTECTED FROM PREGNANCY She should stop the current contraceptive cycle and start a new four-week cycle immediately by putting on a new patch. There is now a new "Patch Change Day" The woman must use back-up contraception for one week	She should take it off as soon as she remembers. The next cycle should be started on the usual "Patch Change Day," which is the day after Day 28. No back-up contraception is needed.

Use after Childbirth

Women who elect not to breast-feed should start contraceptive therapy with the Patch no sooner than 4 weeks after childbirth. If a woman begins using the Patch postpartum, and has not yet had a period, the possibility

of ovulation and conception occurring prior to use of the Patch should be considered, and she should be instructed to use an additional method of contraception, such as condoms, spermicide, or diaphragm, for the first seven days.

Use after Abortion or Miscarriage

After an abortion or miscarriage that occurs in the first trimester, the Patch may be started immediately. An additional method of contraception is not needed if the Patch is started immediately. If use of the Patch is not started within 5 days following a first trimester abortion, she should be advised to use a non-hormonal contraceptive method till she gets her menses.

The Patch should be started no earlier than 4 weeks after a second trimester abortion or miscarriage. When the Patch is used postpartum or post-abortion, the increased risk of thromboembolic disease must be considered.^{6,7}

Sites where the Patch can be applied



The Stomach



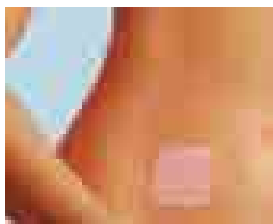
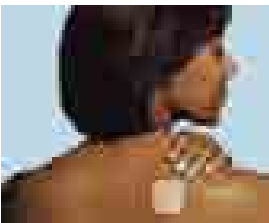
The Upper Arms



The Buttocks



The Back



- Back
- Buttocks
- Arm (outer area), and
- Abdomen
- **Never on breasts**

It can also be used as an **Extended Contraceptive** by avoiding the patch-free week. No withdrawal bleed is experienced.

Adverse Reactions

The side-effects are similar to the use of COC. The most common adverse events reported by 9 to 22% of women using the Patch in clinical trials (n=3,330) were the following, in order of decreasing incidence: breast symptoms, headache, application site reaction, nausea, upper respiratory infection, menstrual cramps, and abdominal pain.

The most frequent adverse events leading to discontinuation in 1 to 2.4% of women using the Patch in the trials included nausea and/or vomiting, application site reaction, breast symptoms, headache, and emotional lability.

Conclusion

The contraceptive patch releasing 20 mcg ethinyl estradiol and 150 mcg norelgestromin is equally effective in suppressing ovulation. Compliance was significantly better with the patch, however, which could lead to improved contraceptive efficacy with long-term use.

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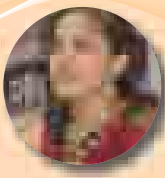
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Chapter 14

Combined Injectable Contraceptives (CIC)



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The name Combined Injectable Contraceptives (CICs) is given to a group of hormonal contraceptives administered by intramuscular injection. The term “combined” indicates that these injectables contain both a progestin and an estrogen as against progesteron only contraceptive (POC).

Deladroxate is a combination of 150 milligrams of dihydroxyprogesterone acetophenide and 10 milligrams of estradiol enanthate. It is still currently sold in some Latin American countries, primarily because it provides more regular bleeding cycles than the lower-estrogen products. However, questions remain about its safety, because of its high doses of hormones, especially estrogen.

The other older combined injectable, known as **Chinese Injectable Number 1**, is a combination of 250 milligrams of hydroxyprogesterone caproate and 5 milligrams of estradiol valerate. This product is used mainly in China.

The new products approved by World Health Organization (WHO), which are becoming more widely used throughout the world, are **Cyclofem & Mesigyna**. These newer combined injectables have been more thoroughly studied than the older products. They are considered better alternatives, because their estrogen content is lower than that of Deladroxate, and the safety of their progestins (DMPA and NET-EN) is well established. These formulations provide very effective pregnancy protection for a 30-day period, therefore, they are also referred to as “monthly injectables”. Currently there are nearly 1 million users of CIC worldwide.^{1,2}

Though 2 new CICs contain precisely the same progestin as the 2 most widely used progestin-only injectables (Depo Provera® and Noristerat); the progestin dose received over time is much lower with the new CICs. The basic difference between CICs and progestin-only injectables (POI) is the presence of estrogen in the CICs;

Table:

Progestin	Natural Estrogen	Brand Names
depo-medroxyprogesterone acetate (DMPA) 25 mg	estradiol cypionate 5 mg	Cyclofem
norethisterone enanthate (NET-EN) 50 mg	estradiol valerate 5 mg	Mesigyna
dihydroxyprogesterone acetophenide 150 mg	estradiol enanthate 10 mg	Deladroxate, Perlutal, Patector, Topasel,etc

the estrogen was incorporated mostly to improve the regularity of the menstrual cycle.

Although CICs and combined oral contraceptives (COCs) are combined hormonal contraceptives, they have several differences.

1. The different route of administration,
2. The presence of a “natural” estrogen in the CICs versus a “synthetic” estrogen in the COCs.

It is known that natural estrogens have very favorable effects on lipid metabolism and cardiovascular function. The addition of a progestin to the estradiol (in CICs) has not been shown to lessen these beneficial effects.

Based on the above evidence, CICs might actually be considered safer than COCs. However, due to the recent introduction of the 2 new CICs, no long-term safety information on the use of these CICs is available yet. Therefore, the current medical criteria for CIC use are mostly derived from the information existing on COC use.

Ideal administration is once every 28 to 30 days, although efficacy has been demonstrated within a 10-day reinjection window (23 to 33 days following the previous injection).³ If a patient presents for a follow-up injection more than 33 days after the previous injection, pregnancy should be ruled out before the drug is readministered.

Efficacy

CIC is highly effective. First-year failure rates in international clinical trials have ranged from 0% to 0.2%.² Large multicenter studies by the World Health Organization

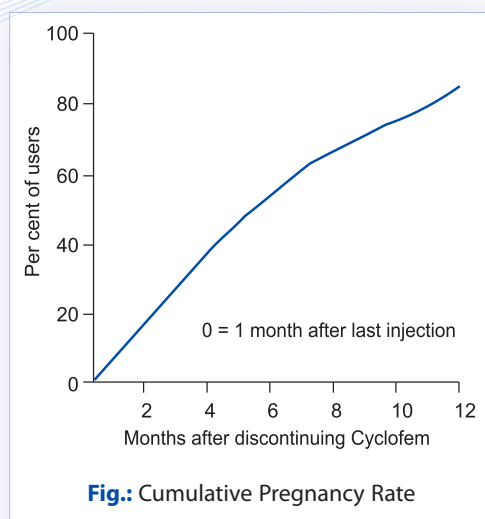
have confirmed the method's efficacy in routine use: among 12,000 women in nine countries comprising more than 100,000 woman-months of experience, a total of five pregnancies were reported (<0.1%).⁴ In a recent US trial, no pregnancies were reported among 782 women using the method for 8,920 woman-months.

Mechanism of action

1. CIC inhibits the secretion of gonadotropins, preventing follicular maturation and ovulation.
2. Thickening and a reduction in volume of cervical mucus
3. Thinning of the endometrium to make it less receptive.

Mean serum concentrations of MPA peak during the first week after administration and remain above the level needed to suppress ovulation for approximately 45 days.⁵

Estradiol cypionate serum concentrations peak about 2 days after injection and decline substantially around day 14.



Return of Ovulation

The contraceptive effects reverse relatively rapidly following discontinuation. MPA is cleared from the body within 60 to 90 days, and ovulation has been observed as early as 63 days after the final injection. Injection site and body weight affect MPA pharmacokinetics and may have an impact on ovulation return.⁵ Return of ovulation may be delayed in lighter women (body mass index ≤ 28) receiving injections. Because combined injectables are effective for a shorter period than progestin-only injectables, their effect is more rapidly reversible

Women who stop using combined injectables may become pregnant as soon as six weeks after their last injection. The fertility rate is over 50% at six months after the last injection and over 80% after one year. Again, remember that the percentage of women having conceived will never reach 100% because, in any population, some women are unable to conceive.

Non contraceptive Health Effects

Users of combined injectables are at no greater risk of developing cardiovascular diseases than non-users.^{6,7} In fact, *Cyclofem* and *Mesigyna* contain natural estrogens, which may have beneficial effects on lipid metabolism and cardiovascular function. The daily dose of estrogen in combined injectables is small, similar to normal estrogen levels in the first half of the menstrual cycle. Thus, estrogen-related side effects are expected to be minimal.

However, long-term information on health effects is not yet available for combined injectables. Therefore, the current contraindications to their use are based

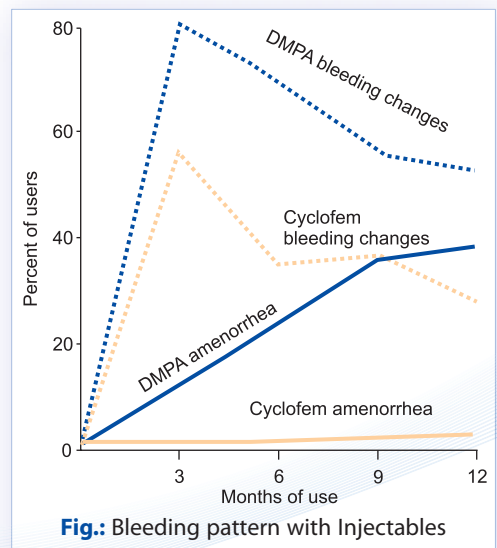
on safety information for combined oral contraceptives, and combined injectables are not recommended for women with conditions that could be affected by estrogen.

Hematologic tests show no significant changes in median hemoglobin. With physiologic dose of estrogen it is unlikely to have an effect on BMD loss.

The most commonly reported side effects are menstrual disturbances

Irregular, frequent, and/or prolonged bleeding

- More frequent during the first year among CIC users compared with OC users, but less likely than POI.
- Bleeding pattern disturbances occur less frequently after the first 3 months of use and continue to decrease over time. Indeed, long-term use tends to produce regular, predictable monthly cycles, similar to the cycle control observed with oral contraceptives.



Source: WHO, 1993.

Overall, 57% of MPA/E₂C users report variations in bleeding patterns during the first 90 days of use, compared with 91% of DMPA users. By the end of the first year, only 30% of MPA/E₂C users show bleeding variations, while the corresponding proportion of DMPA users remains virtually unchanged (92%).

Amenorrhea: As with progestin-only injectables, amenorrhea is managed through counseling. Women should be reassured that amenorrhea does not indicate pregnancy if they have been receiving their injections on time.

How to handle? Counseling

Before the first injection, women should be told to expect bleeding 12 to 15 days after each injection. They should be counseled that menstrual changes are common with combined injectables; especially during first few months and that these changes are not a sign of disease. Administration of ibuprofen or a short course of a combined oral contraceptive may prove helpful.

Other side effects include weight change, breast tenderness, emotional lability, acne, and nausea. In most cases, these side effects are less likely to be reported over time and are not major causes of treatment discontinuation. In a US trial, the 12-month method-related discontinuation rate for MPA/E₂C was under 30%, comparable to the 32% rate observed with oral contraceptives and substantially lower than the 44% who stop using progestin-only injectables during the first year of use. Weight change during 12 months of use varied widely—from 48 pounds lost to 49 pounds gained. Mean body weight change was a gain of 4 pounds after 13 injections and 5 pounds after 15 injections, comparable to the average annual weight gain of 4 to 5 pounds in DMPA users.^{8,9}

Who are ideal candidates for CIC?¹⁰

CIC can be safely opted in all women in whom COC are not contraindicated. (See detailed WHO eligibility guidelines in chapter 3).

WHO criteria for CIC

Category 4: Unacceptable health risk

Category 3: Risks outweigh benefits

Category 2: Benefits outweigh risks

Category 1: No restriction

Advantages of CIC

- Safe, highly effective, easy to use
- Reversible
- Can be discontinued without provider's help
- Can be provided outside of clinics
- Require no action at time of intercourse
- Use can be private
- May have non-contraceptive health benefits like OC pill

Injection Schedule

Woman should receive an injection of a combined injectable once a month (or every 30 days). The window for subsequent injections are up to three days early or three days late. Thus, combined injectables require a more rigid injection schedule than progestin-only injectables. If a woman returns more than three days late, she

can receive an injection if the provider is reasonably sure that she is not pregnant.¹⁰

When is the best time to start CICs?

As with progestin-only injectables, combined injectables can be started at any time during the menstrual cycle, as long as the provider is reasonably sure the woman is not pregnant.

If the first injection is given during the first seven days of the menstrual cycle, no backup contraceptive method is necessary. If the injection is given at any other time, use of a backup contraceptive method for seven days following the injection should be considered.

Combined injectables can be initiated three weeks postpartum if the woman is not breastfeeding. The delay is because the estrogen in combined injectables may promote blood clotting in the early postpartum period.

If the woman is breastfeeding, a delay of six months is recommended. There are no clinical data on the effects of combined injectables on lactation; rather, this recommendation is based on the fact that estrogen in combined oral contraceptives decreases the amount of breast milk produced.

Combined injectables can be initiated immediately post abortions.

Combined injectables contraception is another addition to the contraceptive basket and will help in meeting the unmet contraception need. It has advantage of

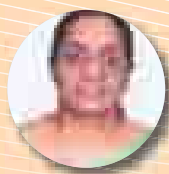
injectable delivery system yet presence of estrogen in low dose & natural form makes it user friendly.

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Chapter 15

Side effects of Combined Oral Contraceptive Pills



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With newer molecules being marketed to avoid the side effects produced by older oral contraceptive preparations, it is necessary to remain apprised of the side effects caused by the “pill” and the effects it may have on various medical conditions.

To enumerate in short, the side effects caused by oral contraceptive pills (OC's) could be major or minor, and they are listed in the table below.

Minor side effects

Nausea, bloating: Found occasionally in a few patients, it is usually not very bothersome. Low fat, low residue, spaced meals, reduce functional nausea. In addition,

changing the OC to high progesterone, low estrogen combination could be tried. The symptoms of bloating or swelling begin in the active week before the hormone-free interval and are most prevalent during the interval.¹

Breakthrough bleeding: Breakthrough bleeding is greatest in the first 3 months and its frequency decreases after that. Low dose oestrogen pills containing 20 microgram or less of estrogen are more likely to produce disorders in cycle control. Pills containing norethisterone produce more irregularities than those containing levonorgestrel.

If the woman could be reassured that bleeding will not reduce contraceptive efficacy no treatment need be given.

Table:

Major side effects	Minor side effects
Increased incidence of CVS diseases, viz venous thromboembolism, heart attack including ischaemic heart disease, cerebrovascular disease or stroke and hypertension.	Breakthrough bleeding, Amenorrhoea
Weak association between long term use of OC and breast cancer diagnosed before the age of 36.	Breast tenderness or fullness
Reduced glucose tolerance	Nausea, abdominal bloating
Cholestasis	Weight gain
Clotting disorders, Pulmonary embolism.	Headache
Abnormal thyroid and adrenal function	Decreased libido, mood changes
Changes in lipid and lipoprotein metabolism	Rarely acne, gum inflammation, increased viral infections, cervical ectropion (which may increase the risk of chlamydia),

However, if it is distressing, to continue to let the woman enjoy the benefits of low dose oestrogen pills, these women could beneficially be given 1.25 mg conjugated estrogen or 2 mg estradiol daily for 7 days when bleeding is present. If 1 course of oestrogen is not enough, another 7 days of estrogen use is effective.²

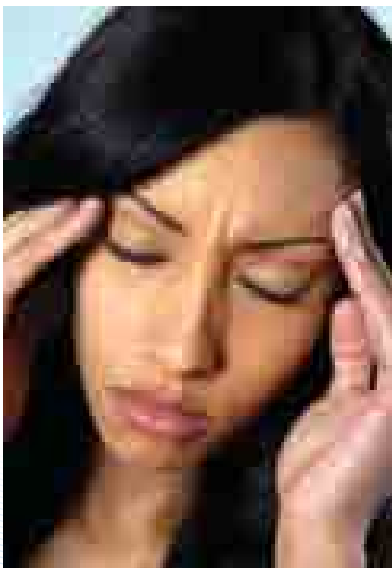
Amenorrhoea: Amenorrhoea is an uncommon side effect found in some women, caused by endometrial atrophy. It is distressing to some women, as it may be a sign of unwanted pregnancy. Addition of extra oestrogen for 1 month (1.25 mg conjugated oestrogen or 2 mg estradiol) daily throughout the 21 days of that cycle will rejuvenate the endometrium and withdrawal bleeding resumes, persisting for many months. This could be resorted to in patients who prefer not to remain amenorrhoeic.²

Headache: Headaches in patients taking COCs may be caused by fluid retention or vascular spasm. Migrainous headaches in OC users frequently occur in the hormone free period, when oestrogen levels are falling. Use of estrogen replacement in

this hormone free period could reduce this symptom. However, women with migraine accompanied by aura are best advised to avoid OC's. Evidence from six case-control studies suggested that COC users with a history of migraine are four times as likely to have an ischemic stroke as nonusers with a history of migraine.³

Weight gain: Weight gain due to water logging caused by progestin content was a common complaint in the past. The current low-dose OC containing 20 µg ethinyl estradiol EE and 100 µg Levonorgestrel LNG did not cause weight gain and was safe and well tolerated in a double blinded placebo controlled trial⁴.

Breast tenderness: Incidence is less with use of low dose estrogen pills. In a study comparing 3 types of contraceptives, participants in the Levonorgestrel containing OC pill group experienced nausea, breast tenderness and irritability more frequently than did those in the other groups, using gestodene and etonogestrel as progestins. Besides changing the type of progestin, shortening the hormone-free interval to 4 or 5 days might also decrease the prevalence of breast tenderness as well as headaches.



Major side effects

Cardiovascular side effects: A WHO study found no increased risk of heart attack among healthy pill users.

Less than 5% of women using hormonal contraception develop hypertension, which may increase their risk for heart attack and stroke.⁵

Thrombotic events: Oral contraceptives (OC) have been implicated in causing increased blood coagulation. The hormone changes during pill ingestion are akin to those occurring in pregnancy and similarly,

the risk of thrombotic events is also present only in the rare individual prone to it (for e.g.; deficiency of some clotting factors, smoking, etc.). The risk posed is actually less than that incurred by pregnancy.⁶

Acute maculo-neuroretinopathy, macular haemorrhage, central retinal vein occlusion, central retinal artery occlusion, and perivasculitis have been reported, mostly in patients on oral pills for a long time. A rare case of central retinal artery occlusion following OC pills has been reported from India after 4 months of use of Mala-D.⁷

The risk of development of deep vein thrombosis was also found to be 2 to 5 times greater with a low-estrogen, desogestrel-containing oral contraceptive than with second-generation monophasic and triphasic preparations⁸ (containing progestin of the norgestrel type). Because desogestrel may have added benefits for some patients, specially women with excessive androgen activity, there is no need to avoid it in normal people not prone to thrombosis.

Risk of cancer: Oral contraceptive use is associated with a very slight increase in breast cancer risk (relative risk=1.2) for current users vs. never-users.¹⁰ However, breast cancer risk associated with the use of oral contraceptives disappears with time when use is discontinued. 1-4 years after discontinuation the relative risk is 1.16, at 5 to 9 years after use the risk is 1.07, and by 10 years from last use, breast cancer risk of ever-users is not different from never-users. It has been found that even in women with familial cancer syndrome, incidence of breast cancer is not higher among oral contraceptive users compared to non-users.

There is an increased incidence of cervical cancer in HPV positive women on prolonged

use of oral contraceptives (>5 years). Till HPV screening becomes cheap and routine, yearly pap smear should be recommended for all women on oral contraceptive pills.

Incidence of ovarian cancer is reduced in OC users and incidence of colorectal cancer is reduced in current users of OCs. There is no increased incidence of hepatocellular cancer and effect on lung cancer is known with use of OC's.

Glucose intolerance: With low dose oestrogen pills, there is just a slight elevation of 1 hour glucose levels. These may be used by diabetic women. However, high pharmacologic dose of estrogen should be avoided by women with diabetes and vascular disease or major cardiovascular risk factors.

Oral contraceptives and medical problems:⁹

Women who should avoid combined oral contraceptive pills:

- Women known to have stones or a positive history for gallbladder disease
- Women with triglyceride levels >250mg/dl and women with existing vascular disease.
- Mitral valve prolapse complicated with atrial fibrillation, migraine headaches, or clotting factor abnormalities.
- Women with congenital heart disease or valvular heart disease if there is marginal cardiac reserve or a condition that predisposes to thrombosis.
- Smokers over 35 years of age
- Women with systemic lupus erythematosus.
- Women with severe diarrhea, as efficacy of the pill will be lost.

Conclusion

The use of newer low oestrogen contraceptives with the use of newer progestins accompanying it have reduced side effects of combined oral contraceptives to a great extent. Most of the studies which showed side-effects of oral contraceptives were done on the earlier preparations with high oestrogen content. However, while using oral contraceptives for dysfunctional uterine bleeding, higher oestrogen doses may have to be employed and in these patients, the practitioner should be aware of all side effects, to take effective steps.

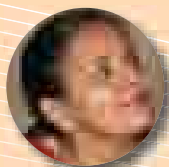
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Chapter 16

Dilemmas in prescribing OC Pills



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“When motherhood becomes the fruit of a deep yearning, not the result of ignorance or accident, its children will become the foundation of a new race.”

Margaret Sanger, 1916.

Though oral contraceptive pill (OCP) is one of the most effective methods of contraception, only 2 percent married women of reproductive age were using oral contraceptives in 1990–2001 (Population reports, 2003) in India. Now with the advent of education and increasing awareness contraception has become the people's movement rather than a force.

While choosing a contraceptive method, the risk of pregnancy is to be balanced against the risk of using contraceptive methods.

Adolescents

According to recent reviews the adolescent age group is increasingly indulging in sexual activities.¹ This group forms an important subset of the population as preventing unwanted pregnancy along with avoiding sexually transmitted infection is an issue in these girls. A dual approach by combining

contraceptive efficacy and protection against PID is offered by OCPs with the use of barrier method.

Though there is concern regarding the effect of OCPs on development of reproductive system and final height achieved in pubertal sexually active girls, there is no evidence regarding the same. It is proven that OCPs do not have any effect on epiphyseal cartilage in the last years of development.²

The awareness regarding the contraception can be improved by adolescent sex education program like FOGSI's Growing Up program.

Patients over 35 years of age

This age group is now increasingly demanding contraception. Though chances of pregnancy start declining after mid to late 30s, contraception is advisable as ovulation continues till menopause. Pregnancy in this group is a high risk one due to increasing medical problems like hypertension, diabetes mellitus etc. This puts forth a dilemma even while considering a suitable contraceptive method for these women. OCPs produce a mild procoagulative effect

by increasing hepatic production of certain clotting factors. As the age increases the risk for venous thromboembolism (VTE) and cardiovascular and cerebrovascular accidents also increases. Despite the fact that these changes occurred in virtually all OCP users tested, VTE remains a rare event. The newer OCPs have slightly higher risk than others. Though the third generation progestins may have a better side effect profile in selected patients due to less androgenicity, **no evidence shows that these agents are clinically superior to 2nd generation progestins.** A thorough personal and family history related to various thromboembolic events should be taken into account prior to prescription of OC pills.

Use of **low dose pills** which do not have any significant effect on lipid profile or abnormal carbohydrate metabolism reduces this risk. **Progesterone only pill (POP) does not show any significant alteration in blood pressures or in blood coagulation factors and provides a good alternative.**

OCPs help these women to avoid pregnancy and to achieve good cycle control, to reduce menstrual disorders like menorrhagia, dysfunctional uterine bleeding and premenstrual syndrome. OCPs also prove beneficial as they reduce the risk of epithelial ovarian carcinoma by 40 percent and of endometrial cancer (56 % after 4 years to 72 % after 12 years of use) and colorectal cancer (37% reduction). It helps to improve the bone mineral density as with hormone replacement therapy.

Initiation of OCPs in the post partum period

There is a concern in this group regarding effect of OCPs on the breast milk volume and quality. POP proves a better alternative as it has a special advantage of being safe

in breastfeeding. In fact several researchers report that POPs appear to increase milk volume.³

In the presence of full breast feeding a contraceptive method should be used beginning in the sixth post partum week. With partial breast feeding or no breast feeding, contraceptive method should be started earlier beginning in the third postpartum week.

In cases of vesicular mole, there was a concern in the earlier years, regarding the use of OCPs as a contraception due to fear of delay in fall of B HCG. Also since Radioimmuno assays were not available interpretation of HCG would be difficult. However this is not a problem anymore. Recent studies have recommended OCPs and POPs after beta HCG level reduces to undetectable levels.⁴

Studies suggest that there is associated 3 fold increase in the risk of diabetes mellitus in women with recent gestational diabetes. This special group should be considered for another method of contraception.

Use of OCs in various medical conditions

Viral sexually transmitted diseases (STD): **Use of OCPs do not protect against STDs. Although barrier contraception reduces risk of STDs, the failure rate of these methods is high (12 to 14 per hundred women years).** Hence for a woman, not in a stable monogamous relationship, a dual approach is recommended. Combining contraceptive efficacy and protection against STD is offered by OCPs with the use of barrier method.

Anti retroviral drugs may reduce the contraceptive effect of OCPs by affecting the drug metabolism or causing nausea

and vomiting. The degree of clinical impact of this interaction, if any, remains to be established.⁶

Bacterial STD: OCPs thicken the cervical mucus and reduce the risk of pelvic inflammatory diseases by 50-60%. This is only seen in patients using OCPs for at least 12 months. The protection is limited to current users only.

Tuberculosis: Tuberculosis is a very common disease in our country. The contraceptive method in this group poses a constant challenge. In patients being treated with rifampicin and isoniazide liver enzymes are induced reducing the contraceptive efficacy of OCPs. Use of OCPs containing higher estrogen dose (50 mcg) and rapid cycling method wherein the woman takes OCPs continuously for three months and then stops. After the withdrawal period the OCP's are restarted. These options improve the efficacy of OCPs.

Consideration of another contraceptive method like IUCD may be advisable as increasing the dose of estrogen can also increase the other side effects associated with OCPs.

Migraine Headaches: Estrogen is thought to increase the incidence of migraine

in susceptible individuals. But low dose formulations can be tried in women with **migraine without aura**. Daily administration can prevent menstrual migraine headaches.

OCPs are best avoided in women with migraine **headaches with aura** or if additional risk factors are present for stroke like old age, smoking or hypertension.

Hypertension: Use of OCPs in hypertensives presents a constant dilemma. Low dose formulations can be used in women less than 35 years with hypertension well controlled on medications. Uncontrolled hypertension and history of atherosclerosis and stroke are contraindications for use of OCPs.

There is no risk of myocardial infarction in women who are normotensive, nondiabetic with use of low dose OCs. The risk of hemorrhagic stroke does not increase in women less than 35 years who are normotensive, but it is 10 times more in women with hypertension. **As POPs do not show any significant alteration in blood pressures, these drugs can be used in this group safely.**

Diabetes Mellitus: OCPs are found to affect the carbohydrate metabolism adversely. OCPs can be used by diabetic females if following conditions are satisfied:

- Less than 35 years old
- Free of diabetic vascular complications or diabetic neuropathy
- Women who do not smoke

However low dose pills can be used in uncomplicated diabetics if proper supervision is provided.

Poly cystic ovarian disease (PCOD): In PCOD patients use of OCPs containing 2nd generation progesterone can worsen the acne and hirsutism. Hence newer



progesterones like cyproterone acetate and drospirinone which are less androgenic are advised. Majority of women with PCOD respond favorably. Metabolic parameters like body weight or glucose tolerance or insulin levels & serum HDL improve in cases of PCOD patients using these newer OCPs.

Elective surgery and oral contraception:

The recommendation that oral contraception should be discontinued four weeks before elective major surgery to avoid an increase risk of postoperative thrombosis is based on data derived from high dose pills

With major surgery and expected prolonged immobilization, prophylactic anticoagulant treatment should be considered for a current user of oral contraceptives. In cases of sterilization procedures it is prudent to maintain contraception right up to the performance of the procedure as this short, outpatient operation carries very minimal, if any risk.

Seizure Disorders: OCPs were thought to exacerbate the epilepsy. Studies have now proved this wrong and in some women improvement in seizure control has occurred.⁵

Antiepileptic drugs that affect liver metabolism, however may decrease the effectiveness of oral contraception. Some clinicians advocate the use of higher dose (50 µg estrogen) products; however no studies have been performed to demonstrate that this higher dose is necessary.

A wiser course is to consider intrauterine contraception with a copper device, long acting methods, barrier methods or sterilization.

Liver disorders: OCPs are contraindicated in patients with active liver disease, cirrhosis or liver tumor. But they can be safely used 6 months after liver disease is cured.

Congenital/Valvular heart diseases: In early days the only contraception recommended in heart disease was a barrier contraceptive. But recent studies recommend low dose OCP in low risk cases.⁶

OCPs are contraindicated only in case of conditions that predispose to thrombosis or in patients with marginal cardiac reserve.

Haematological disorders

Sickle cell disease: A study of erythrocyte deformability in women with sickle cell disease showed adverse effects of contraceptive steroids. But patients with **sickle cell trait** can use oral contraception safely and effectively. According to WHO medical eligibility criteria use of OCPs in sickle cell trait fall in WHO category 2 : advantages outweigh risks.⁷

Lupus erythematosus: Oral contraceptive use can exacerbate systemic lupus erythematosus and the vascular disease associated with lupus. The POPs are a good choice. However in patients with stable or inactive disease without renal involvement OCPs can be considered.

Hyperlipidemia: Because low dose oral contraceptives have negligible impact on the lipoprotein profile, hyperlipidemia is not an absolute contraindication with the exception of very high levels of triglycerides (which can be made worse by estrogen).

OCPs continue to be a very popular method of fertility regulation despite their risks and serious side effects. With ongoing medical research it is possible to identify women who carry substantial risk of this contraceptive method and thus take precautions while using them.

“Since the reality remains unchanged let us change the eyes which look towards reality.”

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