Progestogens in clinical practice, and Hormonal contraception

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Progesterone is a 21 carbon atom steroid compound which is produced by the corpus luteum and placenta. It has the following varied biological actions, which mainly depend on prior estrogen induction of progesterone receptors:

1. Secretory changes and decidual reaction in the estrogen primed endometrium, which causes regularization of cycle.
2. endometrial hemostat, when unopposed estrogenic action in metropathia causes menorrhagia.
3. Menstrual withdrawal on estrogen primed endometrium
4. Decidualization of endometrium and optimal nidation site for the fertilized ovum
5. Endometrial pseudodecidualization and protection against unopposed estrogen induced endometrial hyperplasia and carcinoma endometrium
6. Biological functions optimal for protection and continuation of pregnancy such as endometrial decidualization, myometrial hyperplasia, avoidance of formation of gap junctions and stabilization of lysosomes and myometrial quiescence.
7. Cervical mucus alteration preventing sperm penetration
8. Suppression of gonadotropin secretion and fertility control.
9. Changes in the breast duct-alveolar system and protection against many benign and probably malignant disorders
10. Along with estrogen it can promote bone mineralization and prevent menopausal osteoporosis
11. Relief against spasmodic dysmenorrhoea and premenstrual sydrome
12. Relief against many menopausal symptoms.
13. Thermogenic effect

Progesterone, which is the natural steroid expresses all the above biological actions, but is not orally active and hence is not popularly employed in clinical practice, except as injections or vaginal suppositories for luteal support.

Many progesterone like agents, called progestogens (progestins), have been derived by pharmacological manipulation of progesterone, its esters, testosterone and 19 nortestosterone, and hence have a variety of clinical applications that extend from endometrial hemostasis, cancer protection, contraception to menopausal HRT.

However, all progestogens will not imitate all the actions of progesterone, so much so, the clinician has to identify the most suited progestogen for the situation under question. For example, Duphaston (derivative of progesterone) is good for endometrial decidualization, maintenance of regular menstrual cycles, progesterone challenge and endometrial protection in HRT. But it is a weak hemostat and is not a contraceptive. By contrast the norsteroids (norethisterone, norgestrel or lynestrenol) are effective hemostats and contraceptives and are not used for endometrial decidualization or luteal phase support. Esters of progesterone are particularly employed for decidualization and prolonged progesterone action, such as medical management of endometrial cancer.

The clinician should have clear knowledge of various progestogens available, and their precise clinical applications. A variety of progestogens are available for clinical use, and they should not be considered competitive but each one will have its specific pharmacological application. Hence one progestogen cannot substitute the other for a particular indication. The following will be a working classification of progestogens:

In the most practical sense the progestogens can be classified as those derived from progesterone or those derived from androgen. Those derived from progesterone are duphaston and esters of progesterone, and naturally

they are most progesterone like. Those derived from androgen could be expected to have minimal androgenic ill effects but are more potent in very small doses and have certain specific pharmacological applications such as contraception and hemostasis which the former agents do not generally share.

Classification of Progestogens

1. Plain Progesterone
2. Derivatives of Progesterone
   Duphaston (Dehydroretroprogesterone)
3. Esters of Progesterone
   17 α hydroxyprogesterone acetate
   17 α hydroxyprogesterone acetate 17 n caproate (Proluton Depot)
   6 methyl acetoxy progesterone (medroxy progesterone acetate)
4. Alkyl derivatives of Testosterone
   Ethisterone, danazol and Dimethisterone
5. Alkyl derivatives of 19 Nortestosterone

   i. Estrane Progestins: Norethisterone,Norethisterone acetate and lynestrenol
   ii. Gonane progestins: Norgestrel
   iii. Newer Gonanes: Desogestrel, norgestimate, gestodene

Duphaston: Of all the progestins duphaston has properties closest to native progesterone. It is a derivate of progesterone, called 6 - dehydroretroprogesterone or dydrogesterone, and is similar to endogenous progesterone in molecular structure and pharmacological effects. It reproduces many of the favourable actions of progesterone even in a small dose, but at the same time is orally active Duphaston is progestogenic and is free from estrogenic, androgenic and anabolic effects. It is absorbed rapidly after oral ingestion and urinary excretion of metabolites (dihydroxydydrogesterone) appear in 20 minutes.

Metabolically there is no effect on body weight, blood pressure and blood clotting factors, and cholesterol, VLDL, LDL, HDL or triglycerides are not affected. Adrenal and liver functions are not affected. The only metabolic alteration observed is minimal change in hepatic uptake of insulin which is an inherent action of progesterone, particularly at higher dose.

Its biological effects include decidualization of endometrium for which it is 10 to 30 times more potent than progesterone itself, and it approaches the potency of norsteroids. Complete secretory transformation is possible by 10mg/day for 10 days, with no glandular stromal asynchrony, and thus could cause predictable withdrawal bleeding in estrogen primed endometrium within few days of cessasation of therapy.

DUB: Thus to induce regular cyclical bleeding in an estrogenized anovulatory subject or DUB patient duphaston proves to be the most suitable progestogen. In a dose of 5mg for 5 days it is attended with poor response, 10 mg gives fairly good response, and 20 mg brings about the best decidual response. The standard dose recommended will be 10 mg for 10 to 12 days in the second half of cycle to have optimal cyclical response or withdrawal bleeding. It should be remembered that duphaston is a poor hemostat and hence should never be employed to arrest profuse bleeding in metropathia, where the drug of choice will be the norsteroids such as lynestranol or norethisterone. After including medical curettage with nor steroids, maintenance of regular cyclic bleeding is ideally achieved employing duphaston.

Progesterone challenge: particularly in estrogenized oligomenorrhoeic subjects it is always ideal to employ duphaston to initiate withdrawal bleeding to start CC induction. This is because, the short acting duphaston does not suppress the hypothalamic-pituitary axis and hence CC can induce the necessary endocrine changes favouring ovulation. On the contrary the other agents, such as esters of progesterone (medroxyprogesterone acetate) and norsteroids are less preferred because of their prolonged action on the axis.

HRT: in hormone replacement therapy for premenopausal and menopausal subjects duphaston employed in a dose

of 10 mg for 10 to 12 days of the second half of estrogen therapy has the following benefits: (1) estrogenic endometrial proliferation/hyperplasia is checked, and thus offers endometrial protection; (2) it complements the bone remodeling effect of estrogen; (3) it does not interfere with the favourable effects of estrogen on lipid metabolism and thus proves to be cardioprotective; (4) it does not interfere with the increased production of SHBG caused by estrogen, and thus favours decrease in androgenic ill effects; (5)along with estrogen duphaston decreases the perimenopausal increased levels of homocysteine, and thus proves to be another cardioprotective factor; and (6)it brings about predictable cyclic bleeding.

LPD: Luteal phase defect is usually the consequence of abnormal folliculogenesis, and hence progesterone therapy could help only such situations where the antecedent follicular maturation has been normal. In luteal phase support where there is specific indication for use of progesterone, duphaston can be employed because of its simplicity of administration and quick action.

Dysmenorrhoea: duphaston is not good at axis suppression, and hence is not a contraceptive, but has been successfully used in relief of primary dysmenorrhoea.

Medroxyprogesterone acetate: medroxyprogesterone acetate, or 6-methyl acetoxyprogesterone, has similar actions as duphaston, but being an ester is long acting. This synthetic drugs has increased and prolonged progestational effect and oral efficacy. Their absorpation is rapid, and the half life is approximately 8 hours. For many women a dose of 10mg for 10 to 12 days each month is adequate for endometrial protection. Wherever prolonged axis suppression is aimed medroxyprogesterone is preferable.

HRT: Since medroxyprogesterone has prolonged action it is ideally suited for menopausal HRT where cyclic bleeding is not desired by the patient. In a daily dose of 2.5 mg/day along with low dose estrogen (premarin 0.625mg) administrered continuously, many women could expect to avoid menstrual bleeding while deriving all the benefits of HRT. However, wherever predictable withdrawal bleeding is desired and prolonged axis suppression is to be avoided this agent should not be employed.

DUB and endometrial protection: since it offers good endometrial decidualization and endometrial protection it has also been employed in management of endometrial hyperplasia, in situ cancer endometrium as well secondaries of cancer endometrium.

As duphaston, medroxyprogesterone, acetate is also a poor hemostat, and hence has no role in control of acute episode of bleeding in DUB.

Contraception: By virtue of its prolonged axis suppressing effect, it is a good contraceptive, and has been successfully employed in a dose of 150 mg every month as parenteral therapy.

17 α Hydroxyprogesterone 17-n-caproate: This is another ester of progesterone, which has prolonged action, but is not orally active. In a dose of 250 to 500 mg per week it can offer good endometrial protection and has been employed for treatment of secondaries of carcinoma endometrium. Pregnancy protection has been another indication, but since we do not currently believe in use of progestins for pregnancy support this drug is no more employed.

Derivatives of Testosterone: Ethisterone and Dimethisterone are the derivatives of testosterone, and since they are highly androgenic have no clinical application. The only agent in this group, isoxasol moiety of ethisterone, namely danazol that has been employed for treatment of endometriosis is currently less often preferred. Certainly, the management of endometriosis related infertility is purely surgical and there is no place for medical treatment, with either danazol or GnRH agonist. However, pain relief is certainly an indication of employing these agents, particularly the latter since it has no androgenic side effects.

19 nor testosterone derivatives(19-nor steroids or 19 norprogestins):

The other category of synthetic progestins used are the

19-norprogestins. These androgen derivatives commonly are combined in oral contraceptives because of their increased oral efficacy and increased progestational activity, particularly in a very small dose. They include norethisterone, norethisterone acetate, lynestranol, levonorgestrel, nomegestrol acetate and desogestrel. A variety of noncontraceptive benefits for the combination OC pills, particularly the low dose estrogen-progestin, has been documented. The most sought after is desogestrel in a dose of 150 µg per day along with 30 or 20 µgm ethinyl estradiol.

Of greater concern during long term administration of the 19-norprogestins is their adverse effect on lipoproteins. Many 19-norsteroids lower HDL cholesterol whereas duphaston and medroxyprogesterone acetate do not have any effect on HDL, and this finding may effect the frequency of their use. The newer gonane progestin, desogestrel, however, is "lipid-friendly" and favours increase in HDL-C. it also has excellent bioavailability. Desogestrel in a dose of150µg is efficacious for providing endometrial protection. Hence, OC pills containing desogestrel 150 ug and ethinyl estradiol 20µg can be used to induce cyclical bleeding in perimenopausal subjects being treated for DUB. However, a still lower dose of 10µg of ethinyl estradiol could be a better choice for postmenopausal subjects to avoid the risk of thromboembolism which is more of an hypothetical problem in menopausal HRT with smallest dose of estrogens.

Combination of desogestrel with smaller dose of EE(10 to 20 pgm) should be an ideal alternative for pre and postmenopausal HRT. The extended use of this low-dose oral contraceptive into the late perimenopause will make the change over to a combination menopausal regimen comfortable for many women.

Estranes: estrane and gonane progestins are derived from 19 nor-testosterone, the parent compound used in oral contraceptives. Estranes are characterized by the presence of ethinyl group at 17-α position and by the absence of 19th carbon atom (angular methyl group between the rings A and B) Thus they are essentially 19-nor steroid progestins, and the most widely known compounds are norethisterone (norethindrone), norethisterone acetate and lynestrenol. They are frequently employed as hemostatic progestins for arrest of acute bleeding episodes attended with hyperplastic endometrium in subjects with DUB. These compounds are frequently combined with EE in oral contraceptives,with long track of efficacy and relative safety. However, despite this apparent satisfaction with the estrane progestins the search continued for improved formulations which culminated in the synthesis of gonane progestins.

Nomegestrol acetate: Nomegestrol (2.5 to 3.75 mg) mg/day) is a 19-norprogesterone derivative with potent progestational activity and no androgenicity, has no deleterious effects on body weight, and insulin and glucose levels. Nomegestrol in sequential therapy with oral EE, lowers lipoprotein concentrations, and may limit the effect of oral estrogen on circulating levels of triglycerides.

Gonane Protgestins: The gonanes, e.g., norgestrel, share the structural modifications found in the estranes and in addition possess an ethyl group at position 13. This substitution of methyl radical of norethisterone at 13th position by an ethyl radical markedly increases the progestational and androgenic activity of the molecule, forming a 18,19 dinorsteroid, namely norgestrel. Norgestrel is available as the racemic mixture which contains 50% of levo- and dextro- rotatory principles, with the biological activity confined to levo-norgestrel. This agent is less affected by the first pass metabolism compared to norethisterone, and is more consistent in its action compared to medroxyprogesterone acetate.

The currently employed progestins in OC pills have more than one biologic activity (i) progestational; (ii)antiestrogenic;(iii)androgenic; and (iv)anabolic. The merits of OC progestins are judged on its ovulation inhibiting properties(progestational) activity) and the margin of separation from its other biologic activities. When they are combined with estrogen the other biologic activities may not be manifested. Levonorgestrel has marked progestational and antiovulatory activity at low doses of 250 µg; however, higher doses are required to evoke anabolic and androgenic response. The androgenic properties of levonorgestrel has little clinical relevance when

used at contraceptive doses in combination with EE.

Because OC pills are combination of estrogen and progestin, the clinical effects of these formulations will be an algebraic summation of their biologic activities (biogebraic). The doses have been ultimately reduced in the modern generation minipills to 125 µg of levonorgestrel and 25 mg of EE.

Newer Gonanes (The third Generation Progestins):

The aim of research has been to enhance further "selectivity" for the progestins, namely steroids with further increase in 'desired' progestogenic activity and negligible 'undesired' androgenicity. Of the newer progestins, the newer gonane, namely, desogestrel, appears to match this profile.

The first generation progestins are norethynodrel and norethisterone. The second generation are the other estranes and gonanes. The newer gonanes are the third generation progestins which include desogestrel, gestodene and norgestimate. The newer gonanes also form the fourth major generation of alterations in oral contraception.

Desogestrel is synthesized by the addition of methylene radical (CH2) to the 11th position and forming 3-ketodesogestrel, which is the active principle. By addition of methylene radical to the 11th position, the progestogenic potency of norgestrel could be enhanced and the androgenic potency reduced. Desogestrel is rapidly metabolized in the liver and gut wall to 3β -OH desogestrel (which has estrogenic and androgenic activity). Whenever pharmacological characteristics are attributed, it should be to 3 keto-desogestrel, the physiologically active metabolite.

Desogestrel has a steady half life of 23.8 hours after oral administration. This observation is relevant to noncompliant patients. This newer compound has been developed to reduce the side effects of progestins, such as acne, altered glucose and lipid metabolism, hirsutism, and weight gain. It exhibits excellent contraceptive efficacy and cycle control without significant changes in weight and/or blood pressure.

Selectivity Index: The androgenicity of progestins may be responsible for the following effects of combined OC pills: (I)changes in lipoprotein metabolism; (ii)effects on skin; (iii)increased body weight; and (iv)hypertension. "Selectivity" of contraceptive steroids refers to the ratio between the desired pharmacologic effects and the undesired, other receptor-mediated effects. The desired pharmacologic property of progestins used in OC pill is the progestational activity. The undesired extraneous pharmacology, such as androgenic activity, is not necessary for contraception and serves only to increase the potential side effects. The "selectivity index"(S.I)of a progestin is the degree to which progestational activity is maximized. The SI of various contraceptive progestins as observed in receptor -binding studies show that desogestrel has the maximum of 100 compared to norgestrel 30 and norethisterone 20. The other newer gonane, gestodene (15-levonorgestrel with a double bond between C-15-16), employed in OC in a dose of 75µg, also exhibits excellent contraceptive efficacy and cycle control but has a lower selectivity index of 60 when compared to desogestrel. Similarly norgestimate (250µg)and (25µg) is also an effective contraceptive pill, however, with a relatively low SI.

Receptor binding affinity of progestins: Norethisterone and levonorgestrel have approximately 80% and 40% lower binding affinity respectively, for the progesterone receptors than does desogestrel. The active metabolite of desogestrel, namely the 3-keto desogestrel, has a stronger binding affinity to the progesterone receptor than have other progestins. This may explain the better clinical results and cycle control with desogestrel and low dose estrogen when compared with norethisterone and low dose estrogen. The latter was attended with very poor cycle control.

The affinity of desogestrel for the androgen receptor is markedly less than that of both levenorgestrel and gestodene. Desogestrel and norethisterone show a comparable affinity for the androgen receptor. However, because of the enhanced progestational activity, the OC dose

of the desogestrel is nearly one sixth to one seventh that of norethisterone. Because of the lower dose of desogestrel employed, androgenic exposure of subjects on desogestrel (150μg) is less than one sixth of norethisterone (1mg).

Affinity for Sex Hormone Binding Globulin (SHBG): Desogestrel and norethisterone display comparable distribution over serum proteins and exhibit relatively poor binding affinity for SHBG. Whereas levonorgestrel and in particular gestodene are bound primarily to SHBG with 4 fold greater affinity. Hence the bioavailability of desogestrel is more in the range of 76.1 % to 22.5%.

Favorable effects of desogestrel: Desogestrel has the following metabolic effects which makes the drug not only non-androgenic but also suited for treating hyperandrogenic situations:

i. It does not interfere with the SHBG synthesizing property of estrogenic moiety. In effect SHBG levels in OC pill with desogestrel is 3 to 4 times higher than other progestins in OC Pill.

ii. Binding affinity of desogestrel to SHBG is poor, so much so, there is increased opportunity for testosterone to bind to SHBG, decreasing the free level of testosterone.

iii. Desogestrel is more effective in suppression of ovarian steroidogenesis and by that way also decreases serum testosterone.

It is a potent and safe progestin to be administered for contraceptive and non-contraceptive benefit

i. It is a strong antiovulatory compound even at low doses. Since the dose employed is the lowest, side effects and complications are negligible and clinically acceptable.

ii. Because of the negligible effects on plasma lipids, desogestrel could become an effective alternate to medroxyprogesterone acetate for induction of cyclic menstruation while treating perimenopausal and postmenopausal women.

iii. Moreover in perimenopausal subjects combination of desogestrel 150 μg and ethinyl estradiol 20 μg increases vertebral bone density.

iv. Desogestrel also plays a role of an antiandrogen in women with hyperandrogenic symptoms in need of adequate cycle control and contraception. They include adolescent subjects with acne or hirsutism and PCOS subjects desiring cycle control. It is also favored for symptom relief in mild premenstrual syndrome

Any of the negligible metabolic alterations attributable to desogestrel is offset by the non-relevance in the clinical perspective and the various therapeutic benefits. The biological alterations will not affect the safety of the agent for the adolescent subjects and the reproductively active women who are at low risk for any medical complications. Nor the drug is employed in perimenopausal DUB for more than 6 to 8 months.

Reports on Low dose desogestrel-ethinyl estradiol O.C.:

Lower reliability, loss of cycle control and adverse side effcts on lipid metabolism were thought to occur if the estrogen dose was reduced to lower than the 30μg threshold. However, with desogestrel, the most selective progestin available for use as oral contraceptives, a further dose reduction to 20 μg EE became possible. The present ultra-low dose of EE combined with low dose desogestrel of 150μg has been proved to be a very promising oral contraceptive preparation. This combination is highly effective, provides a good cycle control and ensures an excellent acceptiability.

Only one pregnancy occcurred among 295 women (7257 cycles); incidence of absence of withdrawal bleeding was less than 6% during the initial treatment cycles, gradually decreasing to less than 3% after 20 cycles; the amount of withdrawal bleeding showed no change or a slight decrease; and the incidence of irregular bleeding (spot-

ting or breakthrough bleeding) rapidly decreased from 11.7% after 3 cycles to 8.8% after 6 cycles and less than 5% after 12 cycles; and the preparation was well tolerated with no serious side effects and only 2.7% dropped out because of minor side effects. These results compare well with the currently available 30 µg estrogen contraceptive preparations. In a multicentric study of 10,672 women evaluated for 73,477 cycles, report of only 10 pregnancies speak for the excellent performance of this OC pill. More than 80% had regular cycles, and side effects were few, the most common being headache (<2%), nausea (<6%) and breast tenderness (<6%). There was no significant change in body weight and blood pressure. The pharmacodynamic studies showed increase in HDL and no effect on LDL cholesterol. Serum binding globulin levels increased and serum androgen levels decreased. Measurement of blood FSH, LH, estradiol and progesterone indicated adequate inhibition of ovulation.

The clinical studies prove that the 20µg EE and 150 µg desogestrel combination is as good as the 30 mg EE formulation.

Metabolic safety of hormonal contraception

Hormonal contraceptives produce metabolic effects in addition to their antiovulatory function. Even though higher estrogen dosage and certain androgenic progestins of the 2nd generation are attended with unacceptable metabolic alternations, the current use of low dose EE (20 µg) along with the modern gonane progestin in a low dose (desogestrel, 150 µg) has excellent safety margin.

Protein metabolism:

In general all the 19-norsteroid progestins are known for their inhibitory effects on hepatic synthesis of SHBG, whereas estrogenic compound stimulates hepatic synthesis of SHBG. When both are combined in OC pills the estrogenic effect on SHBG synthesis is suppressed by the norsteroids, and hence generally OC pills result in lowering of SHBG production from the liver. However, this effect is not exhibited by desogestrel, and it does not interfere with estrogenic synthesis of SHBG. So much so, in effect SHBG levels in OC pills employing desogestrel is 3 to 4 times higher. Nor desogestrel has much binding affinity for SHBG. Moreover, desogestrel efficiently suppresses ovarian steroidogenesis. By these three mechanisms more SHBG binding sites are made available for free testosterone, thus leading to a significant fall in biologically active free testosterone. This pharmacokinetic characteristic makes desogestrel as the most suitable progesin for contraception.

Lipid metabolism:

Adverse changes, namely elevation of LDL-C and lowering of HDL-C, have been attributed to certain 19 norsteroids when used in higher doses. However, there is less variation in the lipid levels with low dose 19-norsteroids including levonorgestrel. Hence it is not the progestin per se, but the smallest dose and balanced combination with smaller dose of estrogen that is strategic for improved lipid profile. Desogestrel is more "lipid - friendly" because it does not interfere with the beneficial effects of EE, and it lowers LDL by 14%. Desogestrel containing OC has been found to induce a statistically significant increase in HDL-C in 40% of the observations. Increase in HDL3-C was ensured in 43% of the observations, whereas little effect on HDL2-C was apparent.

Thus desogestrel has distinguished itself from other OC pills through an absence of adverse effects on lipoprotein metabolism and by even allowing for an estrogen induced increase in HDL and decrease in LDL, and this effect is due to the high selectivity of desogestrel.

Carbohydrate metabolism:

Several important findings have become clear: 1. The cardiovascular risk of low - dose OC is substantially lower than that associated with medium - and high - dose OC pills, and most of the risk is caused by thromboembolic events; ii. OC pills may potentiate other well-known risk factors, particularly smoking; iii. Long-term use of OC has little or no impact on development of cardiovascular disease.

All degrees of glucose intolerance have been linked with arterial hypertension, dysliproteinemia, and microvascu-

lar disease. All of these conditions appear to be related to the basic problem of insulin resistance and are clearly linked to increased morbidity and mortality from cardiovascular disease. High levels of insulin may stimulate the sodium potassium adenosine triphosphate pump in the distal tubes of the kidney, thereby causing increased sodium retention and resultant arterial hypertension. In addition, hyperinsulinemia may increase norepinephrine levels and increase sympathetic tone. There also is evidence that insulin causes arterial smooth muscle constriction by affecting the sodium potassium adenosine triphosphate pump in the vessels walls. The genetic defect could result in increased triglyceride synthesis in adipose tissue. Hyperinsulinemia also stimulates appetite and appears to increase levels of very low density lipoprotein. Finally, high insulin levels appear to stimulate arterial smooth muscle proliferation.

Estrogen binds to specific sites on the insulin receptors and prevents degradation of insulin molecule. This action promotes insulin biologic activity and will explain how estrogen actually improves carbohydrate metabolism.

Progesterone and progestins impair carbobydrate metabolism, the impact of which appears to be related to potency, dose and duration of treatment. At high doses most of the progestins, including progesterone esters and norsteroids impair glucose metabolism. For 1 mg dose estrane progestins increase serum glucose by 5 to 10 mg/dl, where as gonanes increase it by 18 to 35 mg/dl. This adverse effect is due to interference with hepatic insulin receptor binding, which results in decreased hepatic uptake of insulin.

The changes in blood glucose and insulin levels of OC pill users, although statistically significant, are usually within the normal range and do not appear to be clinically relevant. The levonorgestrel was shown to have the greatest effect, followed by norethisterone. The impact was mildest for desogestrel after 6 months and after one year, although the changes were within normal limits for healthy women. Hence by employing desogestrel-EE combination the impact on glucose and insulin metabolism could be minimized and that of lipid metabolism improved, a desirable metabolic balance in terms of improved health care measure.

Fat metabolism: Abdominal fat accumulation has been associated with cardiovascular disease and diabetes, whereas gluteo femoral localization of fat is not satistically linked with these diseases. The OC pills have not been associated with significant changes in weight, percentage of body fat or fat distribution, and fat metabolism has been comparable to non-users. This is particularly applicable to desogestrel, and it could also be that body mass and subcutaneous fat are significantly lower when compared to nonusers.

Water metabolism: Theoretically, OC may affect water accumulation through their influence on the renin-angiotensin system. Estrogen induced stimulation of angiotensinogen synthesis by the liver is a possible mechanism. On the other hand, it is also associated with a compensatory significant reduction of plasma renin and prorenin concentrations, suggesting OC induced decreased secretion of these agents by the kidney. In addition progestins may cause water retention, but also has been shown to possess antialdosterone properties. Thus, ultimately there is no proof of water retention or loss during OC use. If at all there is weight gain it is purely due to accumulation of fat.

In conclusion, OC use during the late adolescence and young adulthood is not associated with significant changes in weight, fat distribution and body composition. It should be quite reassuring to these women because of the concern about body image and weight.

Coagulation factors: Over the years the occurrence of vascular events, such as myocardial infarction, stroke, venous thrombosis and thromboembolism, have been minimal as a result of reduction in estrogen dose and improved patient selection. The smallest dose of the newer progestin employed has significant influence on negating the risk of these vascular disorders. This points to the popular use of desogestrel in a dose of 150 μg as the most preferred contraceptive progestin.

Changes in coagulation system has been primarily linked

to the estrogen component of the OC pill, and the risk has been very small on the hemostatic variables, namely, prothrombotic and antithrombotic parameters. The changes induced by 30 µg of EE are generally still less than that observed with 50 µg formulations. With the further reduction to 20 µg EE the safety is further assured to the extent of safe use in perimenopausal and postmenopausal subjects. Desogestrel has the added advantage particularly for the elderly subjects that at 150 µg dose there is no androgenic expression and hence it does not affect the lipid and carbohydrate metabolism.

Noncontraceptive Benefits.

The OCs identify separate from other contraceptive methods by the additional unique advantages it offers for general health care of the individual, namely the "non-contraceptive" benefits. These beneficial effects spread over the entire reproductive life-span and the postmenopausal age of the female, rather from "menarche to menopause". These non-contraceptive benefits must be evaluated particularly in the wider perspective of the noninterference of OCs on lipid, protein and carbohydrate metabolisms as well as on coagulation and weight gain.

Indeed it should be ensured that only the lowest dose regime and the newer progestin alone will be recommended for this purpose. And the most suited will be desogestrel 150 µg, and EE in the range of 10, 20 or 30 µg depending on the age of the patient and the indication for therapy.

The long-term effect of PCOS - associated amenorrhoea appears to be due to lack of cyclic exposure to progesterone and the regular cyclic shedding of endometrium. This is in fact the treatment strategy suggested to avoid endometrial hyperplasia. If ovulation induction is not required, regular low-dose estrogen-progestin combination pill is suggested as the ideal treatment. Combination of EE 20 or 30 µgm and desogestrel 150 µgm could be preferred over other agents.

This combination therapy has the advantage of 1. Lowering of endogenous estrogen excess by axis inhibition, and this could control the endometrial proliferation; 2. Lowering the endogenous androgen excess by axis inhibition, with all benefits of normalization of androgen levels; 3. Regular and normal cyclical bleeding 4. Protective effect on the endometrium; 5. Positive bone metabolism effected by both estrogen and progestin. Alternate approach of oral progestin administration for 12 days every 4 to 6 weeks, employing duphaston or medroxyprogesterone acetate has been advocated. This regime is good for preventing endometrial hyperplasia, but does not offer axis inhibition and control hyperandrogenemia and hyperestrogenism.

Adolescent subjects : Menstrual irregularities, DUB, POCS, acne and hirsutism are the common noncontraceptive indications for perferring OC pill usage. Desogestrel, by virtue of its favourable effect on SHBG and powerful suppression of ovarian steroidogenesis, is the most effetive progestin to exercise anti-androgenic influence. Since there is no increase in body fat or fluid retention there is added advantage of proper body image and normal weight. In adolescent age progestin effect on the lipid and carbohydrate metabolism are less relevant.

EE gives better cyclic control and minimizes the risk of breakthrough bleeding when employed in a dose of 30 µg than the 20 µg which is more suited for perimenopausal subjects in whom the risk of gallstones and thromboembolism should be minimized by smaller estrogen dosage. Moreover, enhanced hepatic synthesis of SHBG could be achieved by higher estrogen dosage, and thus more binding sites could be offered for free testosterone. This antiandrogenic function is more relevant for adolescent subjects.

Since OCs do not interfere with fertility there need not be any apprehension in non-contraceptive usage and the duration of use. It also functions as a profertility agent in PCOS subjects by down regulation of axis for an average period of 3 months. Cyclic administration OC pill for 3 months could precede the ovulation induction protocols. Either spontaneous conception or favourable response to ovulogens have been reported following OC regulation of the reproductive axis.

Women in the third decade: These women derive the benefit of treatment of premenstrual syndrome and protection against early decline of ovarian function. Since the bone mass deterioration starts as early as 35 years, OCs at this age, could prevent the development of osteopenia.

Long term usage certainly offers protection against ovarian and endometrial cancers, with no detrimental effect on breast cancer incidence and cervical cancer. It also prevents the occurrence of benign breast disease.

Perimenopausal subjects: They have the benefit of avoiding menopausal symptoms and bone loss in addition to contraception. Desogestrel, the least androgenic progestin, ultimately proves to have anti-androgenic effect because of its favourable effect on estrogenic synthesis of SHBG and its poor binding to SHBG. Moreover, it effectively suppresses ovarian steroidogenesis. For these antiandrogenic reasons, desogestrel can be confidently prescribed to elderly subjects in a dose of 150 µg, and it has only favourable effects on serum lipids and does not interfere with the "lipid-friendly" attitude of EE.

Thus the only concern should be the altered coagulability of blood, which is the dose depended direct effect of estrogen. The modern formulation with the low dose of EE (20 µg) could solve this dilemma, and is protected against the thrombogenic effect and possibly the risk of gallbladder stones. Hence an accepted combination for peri and postmenopausal treatment and HRT will be desogestrel (150 µg) and EE (20 mg for even 10µgm).

In addition to all these benefits, patient evaluation and regular medical and gynecological surveillance of subjects on OCs immensely benefit the woman from prevention and early detection of any medical or oncological problems.

Oncological benefits: The overwhelming evidence in the literature suggests that use of OCS is not associated with a increase in the risk of breast cancer, regardless of the age and parity of first use or with most of the marked brands and doses. OCs also prevent the occurrence of benign breast disorders.

It was in 1997 that the first hint to the protective effects of OCs against ovarian cancer was made. A risk reduction by about 50% for 4 years of use, which continued for several years after cessation of therapy has been reported. For 7 years use of OCs the risk reduction has been estimated as 60 to 80%. The benefit has been seen to last for upto 15 years of cessation. Even as little as three months of use of OCs could offer some protection against ovarian cancer development.

Similarly, the protective role of OCs in endometrial cancer has now been confirmed beyond dispute. The risk has been reduced by about 40% after 2 years of usage. This protective effect is increased with longer duration of use, and persisted after stopping the pill. Incidence of cervical cancer has no relation to use of OC pills.

Return of Fertility:

One of the myth of hormonal contraception has been that it delays the return of fertility after discontinuation. However, evidences do not support this view, and OCs have no effect on fertility in women who already have atleast one child, and thus the findings are reassuring. Nulliparous women experience a slight delay in returning to fertility, and that too only among older women, but OCs cannot cause any permanent infertility. In fact, anovulatory subjects such as PCOS improve the reproductive status after a course of cyclical hormone therapy. Pill amenorrhoea is usually in subjects who had an underlying axis pathology such as pituitary prolactinoma, and such patients are usually eliminated at the medical workup. For an existing fertility disorder the use of OC cannot be blamed as the cause.