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วิธีการคุมกำเนิดที่ดีนั้นจะต้องมีประสิทธิภาพ ปลอดภัย สะดวกในการใช้มีการยอมรับและใช้ต่อเนื่องกันของผู้ใช้ยาคุมกำเนิดนั้น ๆ ดังนั้นข้อดี–ข้อเสียของการเลือกใช้ยาก็ขึ้นอยู่กับอัตราที่ทำให้เกิดโรคจากยา อัตราตายของมารดาและทารก การเมือง นโยบาย วัฒนธรรมของแต่ละประเทศ

ในประเทศที่พัฒนาแล้ว ยาเม็ดคุมกำเนิดได้ผลดีและมีข้อเสียน้อย ส่วนรายงานอัตราตายที่สูงจากความผิดปกติทางระบบหัวใจและหลอดเลือดนั้นพบในกลุ่มที่สูบบุหรี่มากกว่ากลุ่มที่ใช้ยาเม็ดคุมกำเนิดและอัตราตายจากผลของการตั้งครรภ์ การคลอด และระยะหลังคลอดก็สูงกว่าผลเสียของยาเม็ดคุมกำเนิด นอกจากนี้ยังพบว่าในกลุ่มที่ใช้ยาเม็ดคุมกำเนิดยังทำให้เกิดอักเสบของช่องเชิงกราน เนื้องอกเต้านม การตั้งครรภ์นอกมดลูก ถุงน้ำในรังไข่ การขาดเหล็ก ได้น้อยกว่ากลุ่มที่ไม่ได้ใช้ยา

การใช้ยาเม็ดคุมกำเนิดไม่ใช่วิธีที่ดีที่สุดสำหรับสตรีทุกคน จึงได้มีการใช้ยาฉีด ซึ่งในปัจจุบันนี้มี 2 ตัวที่ใช้กันอยู่ คือ depot medroxy progesterone acetate (DMPA) และ norethisterone oenanthate (NET-OEN) โดยที่ DMPA ฉีดทุก 12 อาทิตย์ และ NET–OEN ฉีดทุก 8 อาทิตย์ใน 4 ครั้งแรก ต่อไปฉีดทุก 12 อาทิตย์ ทั้ง DMPA และ NET–OEN จะไม่รบกวนต่อการหลั่งน้ำนมในสตรีที่ให้นมบุตร แต่ metabolite ของยาโดยเฉพาะ DMPA จะผ่านทางน้ำนมไปทำให้เด็กเกิดอาการตัวเหลืองได้มากกว่า NET–OEN และที่สำคัญก็คือการใช้ DMPA

จะทำให้มีเลือดออกกระปริดกระปรอย ออกมากเกินไป หรือขาดประจำเดือนไป ได้มากกว่าการใช้ NET-OEN

ในอนาคตอาจจะมีการใช้ยาคุมกำเนิดโดยการฝังเข้าผิวหนัง เพื่อให้ยาซึมผ่านตลอดเวลาอย่างช้า ๆ แต่ข้อเสียคือเวลาจะเอาออกต้องใช้การผ่าตัด ดังนั้นถ้าจะให้ดีก็อาจจะให้ผู้ใช้สามารถที่จะใส่และเอาออกเองได้ เช่นการใช้ใส่ทางช่องคลอด และถ้าจะให้ผลดี ยานั้นก็ควรจะค่อย ๆ ปล่อยตัวยาเมื่อมีสัญญาณบอกเป็นระยะในระหว่างรอบเดือน เช่น อาจจะเป็นระดับเอนไซม์หรือฮอร์โมนในกระแสโลหิต

A broad array of contraceptive methods, effective and safe, convenient with simple distribution and administration, with high acceptability and continuation rates and suited to diverse requirements is needed for family planning. This variety is required for a number of reasons:

- major differences in acceptability due to cultural, socioeconomic and religious heterogeneity
- changing needs of couples during the various phases of their reproductive life span and
- great differences in existing national health services [1]

An additional important reason is that not only side effects vary greatly among religiously and ethnically different populations, but also the desired effect regarding pregnancy protection as well as bleeding patterns[2]

Due to a number of genetic, nutritional and other environmental factors metabolism and excretion of administered drugs may differ and there are well-documented ethnic differences in endogenous steroid metabolism when comparing Caucasian and Asian women[3,4]

Significantly different plasma levels have been reported comparing Indian and Swedish women after injection of norethisterone oenanthate[5] but no correlation could be found between the rate of metabolism of norethisterone and the height or weight of the subjects[6]

The risk-benefit ratio of any contraceptive product is affected by disease rates, maternal and infant mortality and morbidity rates, cultural and geographic aspects all of which may vary. Therefore, each country should assess the advantages and disadvantages on its own when selecting which contraceptive to make available to its people[7]

The objectives of this paper are to review the currently available contraceptive drugs on risk-benefit, political issue and future development of new drugs.

Risk–benefit considerations in general

The role of a drug in general and a contraceptive method in particular within the available array of different drugs or methods is determined by its effects and risks. What are the risks of not treating the disease or of not preventing a pregnancy respectively compared to the possible side-effects in a particular population?

For oral contraceptive pills e.g. it is recognized today that in developed countries the risk is negligible for most women especially until the age of 30 years and with-out other predisposing factors and that this risk by far is exceeded by the risks of unwanted pregnancies. In the 1960s and 1970s a substantial body of data was published indicating an excess death rate mainly related to a cluster of cardiovascular complications. But the epidemiological interpretation of these data has been seriously questioned[8] and independent reanalyses of the data revealed that smoking was the primary culprit and that no increase of the relative risk of myocardial infarction morbidity was demonstrable for nonsmoking oral contraceptive users[9,10] Clinical diagnosis of thrombophlebitis–another alleged associated risk–is so uncertain that it cannot form the basis of statistical evaluation[11] Because oral contraceptive pills in women over 35 years not only ensure maximum contraceptive reliability but also pro vide simple, regular control of the menstrual cycle and flow and help to replace the declining stores of oestrogen in women near the menopause, a more flexible approach to pill use in older woman is now advocated also in developed countries[12]

Finally every hazard, whether real or exaggerated, need to be put into the perspective of other hazards which arise from everyday activity that people voluntarily take. As Goldzieher said, the annual death rate for professors who fly a lot in order to give lectures is about 1 in 9,000 per year, and thus it would appear that it is 5 times safer for a woman to take the pill than it is for one to give lectures about it.

It must be stressed now that almost all the published epidemiological investigations have been carried out in wealthy Western countries and it would therefore be quite incorrect to extrapolate the findings to countries in Africa or Asia[13] The death rate of reproductive-age women from complications of pregnancy, childbirth and the puerperium in developing countries is quite high. It was calculated that the risk of death due to the use of oral contraceptives is comparatively much lower even in women with predisposing conditions[14]

When great concern was expressed in developed countries regarding the alleged risk of thrombophlebitis it must be realized that postoperative and idiopathic thrombosis are generally rare events in developing countries. A huge. difference was shown comparing the

incidence of postpartum thrombophlebitis in Rochester, U.S.A. and in Bangkok, Thailand[2]

A drug may have not only negative but also positive side effects.

The magnitude of the preventive effects of the oral contraceptive pill is substantial. When comparing 100,000 women taking the pill with the same number not taking it, one would find yearly

235 fewer cases of benign breast disease

600 fewer cases of pelvic inflammatory disease

120 fewer cases of ectopic pregnancy

300 fewer cases of iron-deficiency anemia and

35 fewer cases of ovarian cysts[15]

Protection against iron-deficiency anaemia may have most important ramifications in developing countries where nutritional levels may be marginal.

Risk – benefit considerations for injectable contraceptives

Despite all their potential inherent benefits, oral contraceptive pills may not be the ideal method for every woman.

An alternate method are injectable depot progestogen contraceptives and there are two available for general use, i.e. Depot medroxy progesterone acetate (DMPA) and Norethisterone oenanthate (NET-OEN).

Depot medroxy progesterone acetate (DMPA) given every 3 months and norethisterone oenanthate (NET-OEN) for which a modified injection schedule is recommended today-every 8 weeks for the first 4 injections interval followed by every 12 weeks.

A multicentric WHO trial comparing DMPA and NET-OEN both administered every 12 weeks found a higher pregnancy rate with NET-OEN, but a better tolerance and cycle control, especially in regards to amenorrhoeas, when compared to DMPA. However preliminary results from a second WHO trial comparing DMPA given every 12 weeks with NET-OEN using a modified injection schedule, i.e. every 8 weeks for the first 4 injections followed by a 12 weeks interval, indicate comparable contraceptive efficacy of these two depot progestagens while maintaining improved bleeding pattern with NET-OEN[16] This modified injection schedule of NET-OEN which requires one more injection per patient treatment is generally recommended today.

These injectable contraceptives may be especially suitable for those women who

- do not tolerate the oestrogen component of the pill or in whom oestrogens are contraindicated,
- are unable to take a pill every day regularly for some social, occupational or educational reasons,
- prefer injections as a more attractive medicine or

- are lactating, because the conventional combined oral contraceptive pills have been shown in many studies to interfere with lactation.

There is an extensive literature now on the metabolic effects of combined oral contraceptive pills. Many of these are related to the dose of oestrogens and they are not found when giving progestogens alone like e.g. long acting injectable contraceptives.[17]

The absence of many of these metabolic effects with DMPA in Thai women was confirmed.[18]

Progestogens are not completely without metabolic side effects however. Weight gain and a moderate diabetogenic and adrenal suppressing effect have been reported especially with DMPA, but probably without much clinical relevance.[17,19]

All progestogens are known to lower the high density lipoprotein (HDL)-cholesterol plasma levels[20] and low levels of HDL are postulated now to be an important indicator for an increased risk of developing atherosclerosis.[21]

From epidemiological studies in Caucasian women a correlation between arterial complications (mortality from stroke and ischaemic heart disease) and progestogens was suggested.[22] But the evidence of these associations in Caucasian women is not conclusive yet, the relevance in Asian women is not known and no comparable studies have been performed in developing countries.

A consideration of practical clinical importance is the effect in women who suffer from fluke infections for countries where this disease is endemic. Reassuring results were reported from Thai women with this disease receiving DMPA, no deleterious effect was found on the metabolic factors studied and on liver function tests.[23]

Both DMPA and NET-OEN were found not to interfere with lactation and may actually improve it[17,24] Another concern when giving a drug to a nursing mother is the possible transfer of this drug or its metabolites to the infant and some studies link neonatal jaundice (hyperbilirubinemia) to the steroid content of breast milk.[25] A plasma : milk ratio of almost 1 : 1 was found among women injected with DMPA, levels of norethisterone in milk were found to be only one tenth or less of those found in plasma.[26] Although large variations occur in the ratio both between subjects and in the same subject at different times it has been suggested to avoid DMPA in lactating women because of its unfavourable milk : plasma ratio.[25] A study in Thai women comparing plasma and milk levels of NET-OEN and DMPA in lactating women to be published soon confirms that the total and daily amounts as well as the duration of transfer into the milk was less with NET-OEN,[27] A study

measuring the levels of NET-OEN in the plasma of breast-fed newborns found that they were undetectable at the time when maximal levels were measured in the mother.[28]

Another positive side-effect has been suggested from studies on the incidence of vaginal mycoses (moniliasis) indicating a protective effect of long acting depot progestogens.[29]

But a major side-effect of these injectables is the disruption of the menstrual cycle found more pronounced with DMPA than with NET-OEN.[30] Excessive and irregular bleeding or spotting as well as amenorrhoea were blamed for the largest proportion of discontinuations in DMPA users and apparently less in NET-OEN users.[31]

Women with menstrual disturbances may be upset because of fear of disease or pregnancy, religious practices, folk beliefs and other rumours. But poor nutrition and short birth intervals in developing countries make regular menstrual patterns the exception rather than the rule and if reassurance is given and fears can be eliminated many women will tolerate e.g. amenorrhoea[31]

The political issue

Rational risk-benefit considerations are sometimes beset by public allegations, politically motivated and based on misleading and erroneous statements. There has been a journalistic tendency of creating sensationalistic reports with emotional and unfounded arguments creating a great deal of worry among laymen and some less informed medical professionals as well. In such an atmosphere of controversy and misunderstanding it is the responsibility of all concerned to dispel an unwarranted climate of fear and to separate science from sensationalism.

A prime example in this context is the ongoing debate on DMPA. The accusation was made to dump a drug into third world countries which is not approved and registered for this purpose in its country of origin. It is true that the U.S. FDA still did not approve its use for contraceptive purpose in the U.S.A., but the reasons given appear to be at least partly unfounded and not to apply necessarily to other parts of the world. The U.S. FDA did not follow a recommendation of its own Advisory Committee on Obstetrics and Gynecology, and the medical experts' panels of such organisations as the WHO, IPPF and U.S. AID recommended its use in family planning programs because its benefits at least in the Third World countries outweigh its risks.[32]

A competent review of the evidence available concluded that DMPA poses no more unresolved problems than oral contraceptives.[33]

DMPA is registered and available now in more than 80 countries, NET-OEN in about 40 countries. Compared to DMPA, NET-OEN so far has been used less extensively and no comparable

controversy has been centred on it. It is registered for contraception in its country of origin, and in the U.S.A. phase III clinical trials are being initiated now supported by a research grant of the National Institute of Child Health and Human Development (NICHD).

Future developments

Development of new birth control technology is a slow progress. To prove safety of new compounds is a time and money consuming enterprise, it takes generally 10-15 years and the expenditure of many million dollars before a scientific discovery can be translated into a widely available birth control agent.[34] The costs of developing a new contraceptive agent have risen so dramatically over the past two decades that they are beginning to outstrip the financial capabilities of an individual company and to reduce greatly the company's chance of recovering such costs after the drug has been approved by the government for marketing in the public. A special feature responsible for the extraordinary costs of fertility regulatory drugs are the long trials required to determine toxicity (unlike those for other drugs) and the very large and long phase III trials in humans, accompanied by an ever-increasing number of follow-up clinical laboratory examinations.[35] Considering furthermore that at present the life span of e.g. U.S. patents is only 17 years, i.e. nearly expiring already when a drug is ready for marketing, it is not surprising that a recent study showed declining activity in research on contraceptive "new chemical entities".[36]

There appears to be little prospect for any new or radically different method to replace existing approaches within the next decade.[37] and instead of research on new chemical compounds there has been an increase in the development of new contraceptive delivery systems using existing contraceptive compounds.[36]

Many of the disadvantages of the presently available injectable depot contraceptives relate to unpredictable pharmacokinetics. Not only is the duration of action rather unpredictable, but the initial plasma levels that are reached are far in excess of those needed for the desired purpose. Thus attempts are being made to achieve a more predictable response both in terms of release rates and duration of action.[38]

Subcutaneous capsule implants of biologically inert substances (like polydimethylsiloxane PDS) filled with a variety of progestational compounds were studied for steady release either through the PDS membrane or from dispersion within a polymer matrix. It was found that tissue reactions occurred causing disorientation of the kinetics of steroid release. Another disadvantage was the need of surgical removal because the device is not degradable.

Another approach is the use of biodegradable polymers as drug delivery systems. The active compound incorpo-

rated into such a biodegradable polymer and distributed evenly throughout the matrix is released at a rate which is entirely dependent on the hydrolysis of the polymer. By the time all of the active drug is released the polymer delivery system also has been completely degraded and therefore there is no need for removal. When these systems are used in the form of micropellets they can be injected intramuscularly. Rods and microspheres made of polylactic-polygycolic acid co-polymers have been used releasing the active compound both via diffusion through permeation and via surface erosion through hydrolytic cleavage of the polymer.

An alternate method allowing the advantage of self-administration and instant self-removal in the case of intolerance, not possible with the previous methods, is a vaginal delivery system such as a vaginal ring. A good contraceptive efficacy was found and the major complaints were menstrual and vaginal problems in clinical trials with a ring releasing levonorgestrel and oestradiol through a silicone rubber overcoat developed by Population Council. The amount of levonorgestrel released daily was considerably higher than contained in a low dosed combined oral contraceptive pill and a significant reduction of HDL cholesterol was found.[39] Vaginal rings developed by WHO contained progestogens only, the most promising one with a release rate of only 20 mcg of levonorgestrel per 24 hours is entering phase II trials now[40]

Finally programmed release systems where the drug will be released only during given times of a menstrual cycle, triggered by a certain signal e.g. through the appearance in the circulation of a certain enzyme or similar, could mimic hormonal plasma levels of a normal menstrual cycle. Such a system could represent a major step forward towards long-acting fertility regulating methods with improved tolerance and acceptability.

Summary

The risk-benefit of contraceptive drugs are reviewed. There are two kinds of available injectable drugs, DMPA and NET-OEN. The latter has less side effects but requires more frequent injections in the first four injections. Development of new drug delivering system is undergoing extensive research, and may be a major step in improvement of fertility control.

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