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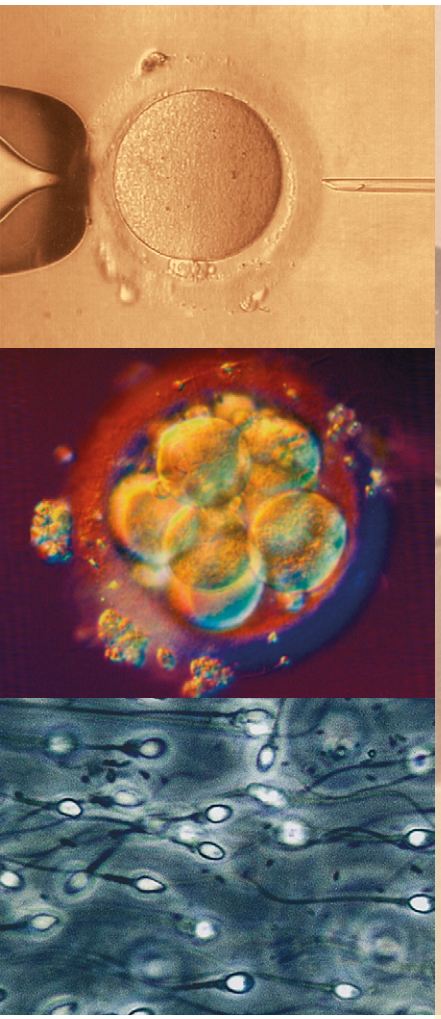

Contraception - Update and Trends

Rabe T

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Contraception – Update and Trends*

T. Rabe

Fertility control in the future will focus on the improvement of existing methods (efficacy, side effects, easy use, duration of action, manufacturing process, costs), on new approaches (mode of action) bringing additional health benefits, and on new targets for nonhormonal contraception. Counselling of women in view to contraceptive choices based on the individual risk (e. g. cardiovascular disease, thrombophilia, family risk of breast cancer, sexually transmitted diseases) will gain more and more importance. Only a few companies can afford research in contraception such as Bayer-Schering-Pharma, and MSD. *Female contraception:* Ovulation inhibition: preselection of patients to minimize the individual risk. New oral contraceptive (OC) regimen, OC with new progestins, OC with estradiol or estradiol esters, new ovulation inhibitors with new progestins and new regimen including long cycles and continuous delivery of steroidal contraceptives, new contraceptive patches, vaginal rings andsprayon contraceptives. Recently identified genes involved in the ovulation process as new targets for ovulation inhibitors. *Fertilisation inhibition:* new intrauterine systems have been developed: a smaller Mirena intrauterine system releasing levonorgestrel (LNG) and a new frameless progestinreleasing intrauterine systems (IUS). Various new contraceptive barriers have been introduced. Research is ongoing on substances acting both as spermicide and as microbicides as a dualprotection method reducing both the risk of unwanted pregnancy and the risk of sexually transmitted diseases. New implantable systems and improved injectables (with improved pharmacokinetic profile, decreased side effects and a safer delivery system) have been made available recently. Various new approaches in female sterilisation include non invasive method of tubal occlusion Immunocontraception for the female will not be available in the near future. *Implantation inhibition:* selective progesterone receptor modulators (SPRMs) are tested for ovulation suppression, morphological changes of endometrium surface inhibiting implantation, postcoital contraception and for longterm use and drug safety. *Male contraception:* Condoms and vasectomy are the only methods available for male contraception. The development of parenteral hormonal contraceptives for men has been stopped recently by the industry but other organizations continue the search for appropriate methods such as combinations of androgen and progestin in implants and also transdermal gels *STD:* Furthermore clients of contraceptive methods must be informed about the risk of sexually transmitted diseases and the way how to prevent them (e. g. safer sex methods). **J Reproduktionsmed Endokrinol 2010; 7 (Special Issue 1): 18–38.**

Key words: contraception, family planning, fertility control, female, male, ovulation, fertilisation, implantation, spermatogenesis

Introduction

According to projections of the United Nations (UN) and the World Bank, 80–90 % of population growth until 2025 will occur in developing countries; 50 % of population growth is based on increasing life expectancy attributed to e. g. better medical care, 17 % of couples are wishing for more than two children and 33 % of the population growth stems from unwanted pregnancies.

The demand for fertility control is expected to increase within the next two to three decades as the number of couples in the reproductive age groups in developing countries alone is expected to grow to nearly 1 billion. The situation in most developed countries is quite different: e. g. in Germany, there is a ratio of 1.3 children per couple, which is far below the threshold value of 2.1 necessary for maintenance of the population size and to guarantee the retirement funds for the elderly.

- **Internet Links**
- United Nations Population Fund – UNFPA, the United Nations Population Fund (http://www.unfpa.org)
- The world's growing population [PDF] (http://wbln0018.worldbank.org/HDNet/hddocs.nsf/65538a343139acab85256cb70055e6ed/8ebf48e0f2ac79c385256e00005eb785/$FILE/Growing%20Population.pdf)
- WHO, Geneva, Switzerland (http://www.who.int/reproductivehealth/en)
- The World at Six Billion United Nations – Introduction [PDF] (http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf)
- World population – Wikipedia, the free encyclopedia. Current projections by the UN's Population Division (http://en.wikipedia.org/wiki/World_population)
- United Nations Statistics Division – Common Database Population annual growth rate, estimates and projections (annual, 1950 to 2050) (http://unstats.un.org/unsd/cdb/cdb_dict_xrxx.asp?def_code=379)

Contraceptive Use and Techniques

The prevalence of contraceptive use is increasing worldwide, and in many countries over 75 % of couples use effective methods. However, existing methods of contraception are not perfect, do not fit all couples and their acceptability is limited by side effects and inconvenience. Even in some developed countries where contraception is freely available, many unplanned pregnancies occur. There is thus a real need for new methods of contraception to be developed that are more effective, easier to use, and safer than existing methods.

Demographic forces, prevalence of disease, and social and cultural factors influence not only the use of contracep-

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tives but also the development of new methods. The age of onset of sexual activity is decreasing, while childbearing is being delayed or, in many developed countries, forgone altogether. There is public pressure for the use of more "natural products", which are perceived to be safer, but at the same time contraceptives are expected to have almost perfect efficacy.

The development of new and improved methods of contraception for both women and men is a key component of the strategy to improve the quality of family planning programs. Family planning clients are often restricted by the choice of methods offered to them, or are deterred from using contraception due to the side effects related to use of available methods. The crucial issues in the future will therefore be aimed at optimizing the use of currently available methods and making them safe, effective, and acceptable, with minor alterations in composition or delivery system. In addition, there should be new developments in contraceptive technology to improve compliance and satisfy the unmet needs.

Contraceptive choices can be classified according to their mode of action and the duration of use (reversible and permanent methods).

Requirement for New Contraceptives

The requirements for new contraceptives include:

- good contraceptive efficacy (female [f]/male [m]),
- good control of the menstrual cycle (f),
- no side effects (f/m),
- reversible (f/m),
- no negative effect on libido (f/m),
- easy to use (f/m),
- not expensive (f/m),
- worldwide availability (f/m),
- worldwide acceptable based on religious, political, and ethical considerations (f/m),
- offering "non contraceptive benefits" (f/m) with increasing interest, e. g. no influence on body weight (f/m), no risk for breast cancer (f) or prostate cancer (m), positive effect on skin and hair (f/m), no or decreased menstrual bleedings (f), improvement of dysmenorrhoea (f), improvement of premenstrual syndrome (f)

Research in the Field of Contraception

Research on new contraceptives is only done by Bayer-Schering-Pharma, and Organon (now MSD); generics are mainly produced by Barr Laboratories, US. To find one new substance more than 5000 drugs need to be tested over 10–15 years, costing 400–800 million US Dollars. Both Wyeth, bought by Pfizer, and Ortho McNeil have stopped the research in the field of contraception.

According to the WHO (World Health Organisation, Geneva, Switzerland) fertility control in the future will focus on [1]:

1. Improvement of existing methods: efficacy, side effects, duration of action, manufacturing process, costs
2. New approaches: more selective mode of action
3. New targets for contraception

In this paper, the authors will describe the actual knowledge on fertility control and possible future aspects based on the various targets for contraception in women and men.

- **Internet Link**
  – Family planning, contraception: Guidelines, reviews, position published by the Geneva Foundation for Medical Education (http://www.gfmer.ch/Guidelines/Family_planning/Family_planning_contraception.htm)

Female Contraception

Contraceptive methods for women can be classified according to the inhibition of ovulation, fertilisation and implantation, respectively.

For some of the contraceptive methods a Cochrane analysis is available. But this analysis can only be as good as the underlying studies are. Because of the importance of placebocontrolled randomized trials that cannot be conducted for contraception purpose, most of these studies are open and must be carefully analysed in view to e. g. sample size, origin, selection, performance of the study, dropouts and other bias – which may lead to wrong conclusions (e. g. Women's Health Initiative Study).

Ovulation Inhibition

The release of the female germ cell, the ovum, from the ovary is a key event in mammalian reproduction. Ovulation is a complex process that is initiated by the luteinizing hormone surge and is controlled by the temporal and spatial expression of specific genes.

Ovulation inhibition can be achieved by oral hormonal contraceptives (100 million women worldwide) [2], hormonal patches (1 million users worldwide), vaginal rings (3 million users worldwide), estrogenfree progestin formulations (2 million users worldwide), once-a-month injectables (2 million users in Middle and South America), and prolonged breastfeeding (100 million women worldwide) (personal information Bayer-Schering-Pharma 2007 and Organon 2007).

Oral Hormonal Contraceptives

Update

Oral hormonal contraceptives (combined or sequential estrogen/progestin formulations) have been available since 1959 (Enovid/Synthex/US) and as Anovlar (Schering/Germany) since 1961 (Europe).
Composition: OCs contain either progestins derived from 19-nortestosterone as 1st (norethisterone, norethisterone acetate, lynestrenol, ethinodiol diacetate, 2nd (levonorgestrel) or 3rd generation (desogestrel, gestodene, norgestimate) or new nonethyl estranges with antiandrogenic properties (dienogest), derivatives of 17-hydroxyprogesterone (e. g. chlormadinone acetate, cyproterone acetate) or spirolactone derivates with high antimineralocorticoid properties (drospirenone) and 15–35 µg ethinylestradiol (EE) per tablet. New generations of OCs containing Estradiol (E_2) rather than EE are reaching the market and are based on new progestins such as dienogest, or new 19-norprogesterone derivatives such as or nomegestrol acetate (for oral use in OCs) or Nestorone® (for nonoral use combined with E_2 in transdermal gels).
Indication: Oral hormonal contraceptives can be used for fertility control but also for various medical reasons e.g. treatment of disturbances of the menstrual cycle, dysmenorrhoea, premenstrual syndrome (PMS) and acne vulgaris.

Acne vulgaris

In Germany there is a high incidence of at least mild types of acne vulgaris and

seborrhoe (40–60 % of all women aged 15–25).

OCs with antiandrogens (cyproterone acetate, chlormadinone acetate, dienogest, and drospirenone) are preferred by more than 60 % of all women in the reproductive age (personal information Bayer-Schering-Pharma, 2007), but mild acne can also be improved by using various oral contraceptives. In a Cochrane analysis [3], Arowojolu AO et al. found 23 trials dealing with birth control pills and acne: 5 trials used 'dummies', 17 compared different types of birth control pills, and 1 compared a pill and an antibiotic. The three pills studied in trials with dummies worked well to reduce facial acne. In comparing pills with different hormones, no important differences were seen.

OC and brain

OC may lead to mood changes. Depressive mood and premenstrual syndrome (PMS) occur quite frequently in various female populations (incidence of mild PMS 30–80 %; incidence of moderate PMS 20–40 %). The incidence of the severe type of the disease, the premenstrual dysphoric disease (PMDS) is 2–9 % [4–7].

Depressive mood occuring in patients with premenstrual syndrome may improve using oral contraceptives; an ex tended cycle may offer some advantages, too.

A 24 day regimen with drospirenone called "YAZ" was approved in the US in 2005 for the treatment of emotional and physical symptoms of premenstrual dysphoric disorder (PMDD), which is a severe form of premenstrual symptoms. In Europe YAZ is available since 2008.

Depressive mood in OC users might be due to a deficiency of vitamine B6.

Exclusion of risk factors

Cardiovascular risk factors

Family history in view to cardiovascular disease is gaining more and more importance, in view to find out women at risk. The family history includes deep vein thrombosis, thromboembolism, cerebral stroke in the parents (< 45 years), myocardial infarction (mother < 45 years), and any of these diseases in brothers and sisters of the patient. Furthermore the patient history in view to cardiovascular events is important.

The following laboratory tests for thrombophilia can be performed if indicated: e. g. Factor V-Leiden gene, prothrombin polymorphism, plasminogen activator inhibitor (PAI) polymorphism, antithrombinIII, protein C, protein S, Factor VIII, homocysteine, and if elevated MTHFR gene (methyltetrahydrofolate acid reductase).

The individual risk in relation to thrombophilia can be analysed and the patient can be counselled with regard to the risk of contraception and lifestyle (e. g. longdistance travel).

Side effects

OC and body weight

The body weight is a very important factor for female self esteem and wellbeing.

Various OCs lead to changes of the body weight in new users of plus/minus 1–2 kg depending on e. g. the annual season the user starts the pill, the initial body weight, psychological factors etc.

The impact of OCs on the body weight doesn't depend on anabolic effects; steroid hormones can enhance the appetite; ethinylestradiol may lead to water retention in soft tissue.

Drospirenone containing OCs may lead to a decrease of body weight in new users by up to 0,5 kg in the first six months with an increase up to values observed with other OCs thereafter. However this weight change is related to water excretion due to the antimineralocorticoid effect of the progestins as compared with other OCs inducing water retention is most users.

In a Cochrane analysis Gallo et al. [8] found that contraceptives pills and patches do not lead to major weight gain. The 3 placebo-controlled, randomized trials did not find evidence supporting a causal association between combination oral contraceptives or a combination skin patch and weight gain. Most comparisons of different combination contraceptives showed no substantial difference in weight. In addition, discontinuation of combination contraceptives because of weight gain did not differ between groups where this was studied (see also [9]).

Bone density and fractures [10]

A higher BMD and a larger bone size attained in childhood and maintained through the third decade of life has been related to a subsequent reduction in the risk of childhood fracture, stress fracture, osteoporosis and fractures related to osteoporosis later in life. Therefore, it is important to understand factors that can be modified to improve the accrual of peak bone mass and increase the bone size in women. Factors that may positively influence BMD are high levels of physical activity and adequate calcium intake.

Genetic factors account for 60–80 % of the variance in peak bone mass. Failure to achieve the genetically predetermined complement of bone mass is often related to suboptimal environmental and lifestyle conditions in women. Bone accrual can also be limited by eating disorders and oligo and amenorrhea. Oral contraceptive (OC) use may have an effect on bone accrual but its exact role is unclear.

Oral contraceptives

There is some evidence attributing a modest benefit of oral contraceptive use to spine and hip BMD. Alternatively, several recent studies have shown either no effect or negative effects of oral contraceptives on bone density. The impact of OC on bone size is not well understood either.

The type of contraception, age at first use and level of exercise may alter the impact of OC use on bone health.

Observational studies of OC use on bone mass may be confounded by the underlying reason for use as 4–9 % of women use oral contraceptives for reasons other than birth control, including amenorrhea or oligomenorrhea.

A recently published study of female military cadets has shown that the use of oral contraceptives is linked with loss of bone density in women. The study examined the effects of lifestyle, diet, and exercise on bone health of 107 white female cadets at the United States Military Academy in West Point, New York, and found that irregular menstruation and oral contraceptives had a negative impact on bone density [10].

In adolescents there is a slight diminishment of bone mineral density but no higher fracture rate. Also this question must be clarified for OCs on the market and for new products.

Oral contraceptives and cancer
A recent review dealing with hormonal contraception and cancer in women has been just published by [11]. A reprint of this paper is also published in this supplement.

Breast cancer
– Incidence: The incidence of breast cancer is worldwide increasing; one of ten women will suffer from breast cancer during life time.

Risk factors are analysed in various reviews (e. g. [12], (http://info.cancerresearchuk.org/cancerstats/types/breast/riskfactors). According to Fletcher [13]:
– Strong risk factors are increasing age, family history, previous breast cancer.
– Moderate risk factors are density of the breasts on mammogram, biopsy abnormalities, exposure to radiation.
– Other risk factors: age at time of reproductive events, pregnancy and breastfeeding, hormone replacement therapy (HRT), height and weight, alcohol consumption, presence of other cancers, miscellaneous factors.
– Decreasing the risk are removal of the ovaries, lifestyle changes, medication, early detection.

A reanalysis of worldwide epidemiologic data on the possible relationship between OCs and the diagnosis of breast cancer had been conducted 1996 by the Collaborative Group on Hormonal Factors in Breast Cancer. The reanalysis involved 54 studies (90 % of all epidemiological studies), a total of 53,297 women with breast cancer and 100,239 women without breast cancer [14].
Results of this reanalysis:
– Breast cancer risk: Women who were current or recent users of birth control pills had a slightly elevated risk of having breast cancer diagnosed.
– Age and risk: The risk was highest for women who started using OCs as teenagers.
– Risk after OC withdrawal: However, 10 or more years after women stopped using OCs, their risk of developing breast cancer returned to the same level as if they had never used birth control pills, regardless of family history of breast cancer, reproductive history, geographic area of residence, ethnic background, differences in study design, dose and type of hormone, or duration of use.
– Course of disease: In addition, breast cancers diagnosed in women after 10 or more years of not using OCs were less advanced than breast cancers diagnosed in women who had never used OCs.
– Excess number of cases: The breast cancer incidence in young women is low and rises steeply with age. The estimated excess number of cancers diagnosed in the period between starting use and 10 years after stopping increases with age at last use: for example, among 10,000 OC users from Europe or North America who used oral contraceptives from age 16 to 29, the estimated excess number of cancers diagnosed up to 10 years after stopping use rises from 0.5–4.7.

The Reanalysis by the Collaborative Group on Hormonal Factors in Breast Cancer 1996 [14] is based on data with older high-dose combined oral contraceptives used between 1976 and 1996 whereas today worldwide low-dose pills are used.

In a big casecontrol study Marchbanks et al. [15] interviewed a total of 4575 women with breast cancer and 4682 controls who were 35–64 years old. The relative risk was 1.0 (0.8–1.3) for women who were currently using oral contraceptives and 0.9 (0.8–1.0) for those who had previously used them. The relative risk did not increase consistently with longer periods of use or with higher doses of estrogen. The results were similar among white and black women. Use of oral contraceptives by women with a family history of breast cancer was not associated with an increased risk of breast cancer, nor was the initiation of oralcontraceptive use at a young age. In conclusion among women from 35–64 years of age, current or former oralcontraceptive use was not associated with a significantly increased risk of breast cancer.

More recently, the results of the Royal College of General Practitioners Study in the UK were published. From 1968 to 2007, the study followed 46,000 women who had either used or never used OCs, comparing their mortality rates. The four decades of data showed that there was a small decrease in the mortality rates of women who had taken the pill, as well as a small decrease in the overall risk of developing cancer. The authors concluded that oral contraception was not associated with an increased long-term risk of death in this large UK cohort; indeed, a net benefit was apparent. The balance of risks and benefits, however, may vary globally, depending on patterns of oral contraception usage and background risk of disease [16].

Even in patients with high family history risk for breast cancer and in carriers of BRCA1 mutation OC seem to have no negative influence of the breast cancer incidence in those subjects [17, 18].

The question why in OC users there is a higher detection rate of breast cancer (earlier detection of preexisting tumours) or a higher life-time risk (additional new tumours in OC users) has not settled until now. A stimulation of preexisting breast cancer is assumed, rather than induction of mutagenesis and new tumours (latency between exposition towards a noxe and clinical detectable carcinoma: 10–15 years).

In postmenopausal women the lower incidence of HRT use led recently to a lower rate of breast cancer cases diagnosed.

Regular cancer screening including self examination of the breasts is strongly recommended.

Ovarian cancer
– Epidemiology: Second most frequent genital tumour of women in Germany.
– Incidence: New cases 15/100,000, maximum at age 50–60 years; age 45: 40/100,000; age 70: 50/100,000. In 2 of all cases first diagnosis in FIGO stage III and IV.
– Risk factors: High risk situation in cases with genetic predisposition (BRCA1 and 2); approx. 10 % of all cases.

According to the Holden Comprehensive Cancer Center, Cancer Information Service (2003): The risk factors that are known to increase the chance of developing ovarian cancer are family history, hormone replacement therapy, talcum

powder, fertility drugs, high fat diet. The protective factors for ovarian cancer are: oral contraceptives, childbearing and breastfeeding, tubal ligation and hysterectomy.

Studies have consistently shown (National Cancer Institute, US) (www.cancer.gov/cancertopics/factsheet/Risk/oralcontraceptives):

- Duration of use: OCs reduce the risk of ovarian cancer. In an analysis of 20 studies of OC use and ovarian cancer, researchers from Harvard Medical School found that the risk of ovarian cancer decreased with increasing duration of OC use. Results showed a 10 to 12 % decrease in risk after 1 year of use, and approximately a 50 % decrease after 5 years of use [19].
- Amount or type of hormones in OCs: One of the studies used in the Harvard analysis, the Cancer and Steroid Hormone Study (CASH), found that the reduction in ovarian cancer risk was the same regardless of the type or amount of estrogen or progestin in the pill [20]. A more recent analysis of data from the CASH study, however, indicated that OC formulations with high levels of progestin reduced ovarian cancer risk more than preparations with low progestin levels [21]. In another recent study, the Steroid Hormones and Reproductions (SHARE) study, researchers investigated new, lower-dose progestins that have varying androgenic properties (testosteronelike effects). They found no difference in ovarian cancer risk between androgenic and nonandrogenic pills [22].
- IACR analysis (1999) (http://www.inchem.org/documents/iarc/vol72/vol721.html): 4 cohort and 21 case-control studies addressed the relationship between ovarian cancer and use of combined oral contraceptives.
- Duration of use: Overall, these studies show a consistent reduction in the risk for ovarian cancer with increasing duration of use. The reduction is about 50 % for women who have used the preparations for at least five years, and the reduction seems to persist for at least 10–15 years after use has ceased.
- Histology: A reduction in risk for ovarian tumours of borderline malignancy is also observed.
- Low-dose formulations: Few data are available on the more recent, low-dose formulations.
- A published case-control study in the US showed a 38 % lower risk for women who took high estrogen and progestin pills and a 81 % lower risk for those taking low levels of both hormones [23].
- Genetic risk factors: OC use in women at increased risk of ovarian cancer due to BRCA1 and BRCA2 genetic mutations has been studied. One study showed a reduction in risk, but a more recent study showed no effect [24, 25].

Endometrial cancer

A metaanalysis by the IACR (1999) included three cohort and 16 casecontrol studies which addressed the relationship between use of combined oral contraceptives and the risk for endometrial cancer. The results of these studies consistently show:

- Risk reduction: The risk for endometrial cancer of women who have taken these pills is approximately halved.
- Duration of use and persistence: The reduction in risk is generally stronger the longer the oral contraceptives are used and persists for at least 10 years after cessation of use.
- Low-dose formulations with new progestins: Few data are available on the more recent, low-dose formulations.

Use of sequential oral contraceptives which were removed from the consumer market in the 1970s was associated with an increased risk for endometrial cancer.

Cervical cancer

National Cancer Institute, US (www.cancer.gov/cancertopics/factsheet/Risk/oralcontraceptives):
Increased risk: Evidence shows that longterm use of OCs (5 or more years) may be associated with an increased risk of cancer of the cervix [26].

HPV as main risk factor: although OC use may increase the risk of cervical cancer, human papillomavirus (HPV) is recognized as the major cause of this disease. Approximately 14 types of HPV have been identified as having the potential to cause cancer, and HPVs have been found in 99 % of cervical cancer biopsy specimens worldwide [26]. More information about HPV and cancer is available at http://www.cancer.gov/cancertopics/factsheet/risk/HPV.

Further risk factors are chlamydia infection [27] and cigarette smoking [28].

An analysis by the International Agency for Research on Cancer (IARC) (2003) found:

- An increased risk of cervical cancer with longer use of OCs. Researchers analyzed data from 28 studies that included 12,531 women with cervical cancer.
- The data suggested that the risk of cervical cancer may decrease after OC use stops [29].
- In another IARC report, data from eight studies were combined to assess the effect of OC use on cervical cancer risk in HPVpositive women. Researchers found a fourfold increase in risk among women who had used OCs for longer than 5 years. Risk was also increased among women who began using OCs before age 20 and women who had used OCs within the past 5 years [30].
- The IARC is planning a study to reanalyze all data related to OC use and cervical cancer risk [26].

Regular cancer screening including cervix cytology is strongly recommended.

Liver cancer

Summary according a recent statement of the National Cancer Institute (US) (www.cancer.gov/cancertopics/factsheet/Risk/oralcontraceptives):

- Several studies have found that OCs increase the risk of liver cancer in populations usually considered low risk, such as white women in the United States and Europe who do not have liver disease. In these studies, women who used OCs for longer periods of time were found to be at increased risk for liver cancer.
- However, OCs did not increase the risk of liver cancer in Asian and African women, who are considered high risk for this disease. Researchers believe this is because other risk factors, such as hepatitis infection, outweigh the effect of OCs [31].

Various cancer risks

A recent online publication in the British Medical Journal by Hannaford [32] is

concerned with the overall cancer risk of oral contraceptives. Taking the contraceptive pill does not increase a woman's chances of developing cancer and may even reduce the risk for most women. This is the conclusion of researchers who analysed the UK cohort data spanning a 36-year period from the Royal College of General Practitioners' oral contraception study, which began in 1968. The accompanying editorial by Meirik and Farley [33] makes the point that in a developed country with an effective cervical cancer-screening programme, the pill is a safe contraceptive method with respect to cancer. In some developing countries with inadequate cervical cancer screening and healthcare services, and high cervical cancer rates the balance of cancer risk is probably less favourable.

Reduction of ethinyl estradiol dosage

- Lowering the ethinyl estradiol (EE) dosage per tablet from 50 to 30–35 µg led to a reduction of myocardial infarction, stroke and deep vein thrombosis (DVT).
- Lowering the ethinyl estradiol (EE) dosage per tablet from 30–35 to 0 µg per tablet led only to a further reduction of DVT.
- Lowdose pills (20 µg versus > 20 µg ethininylestradiol/tablet) [34]: In this Cochrane analysis the studies found that more women taking the pills with less estrogen quit the studies early and that they had more disruptions to bleeding patterns than the women using the pills with more estrogen. This review was not able to study differences in the low-estrogen pill ability to prevent pregnancy.
- Estrogen-free contraceptives: (Cerazette; MSD): Apart from inducing a local barrier, an estrogen-free contraceptive in addition reliably suppresses ovulation. Ovulation was inhibited in 97 % of cycles at 7 and 12 months after initiation. The Pearl Index was 0.14 per 100 woman years, which is significantly lower than a pearl index of 1.17 found for levonorgestrel-only pill. Pearl indices of the desogestrel POP and of COC have not been compared directly. At begin of the treatment there was a higher incidence of amenorrhoea and irregular bleedings in the group receiving the desogestrel-only pill when compared to the levonorgestrel-only pill. After several months the number of irregular bleedings in the desogestrel-only group decreased [35]. Cerazette can also be used by breast feeding women and can be used as normal oral contraceptive with a delay up to 12 hours if somebody forget the regular intake of the pill. The major disadvantages are continuous and unpredictable irregular bleedings in some of the women.

Regimen of oral contraceptives

- Biphasic vs monophasic oral contraceptives: in a Cochrane analysis van Vliet et al. [36] did not find enough evidence to say if 2-phase pills worked any better than 1-phase types for birth control, bleeding patterns, or staying on the pill. The one trial report had method problems and lacked data on pregnancies. Therefore, one-phase pills are the better choice, since we have much more evidence for such pills and two-phase pills have no clear reason for use. *(Author's comment: weak Cochrane analyis due to lack of data).*
- Biphasic vs triphasic oral contraceptives: in a Cochrane analysis [37] showed that available trials did not provide enough evidence to say if 3-phase pills worked any better than 2-phase types for birth control, bleeding patterns, or staying on the pill. More research would be needed to show whether 3-phase pills were better than 2-phase pills. However, 2-phase pills are not used enough to justify further research. *(Author's Comment: weak Cochrane analyis due to lack of data).*
- Continuous daily regimen for 3 months: In the US two 3-months pill are available: Seasonale (84 days 30 µg ethinylestradiol/150 µg levonorgestrel)/7 days hormone-free. Seasonique (84 days 30 µg ethinylestradiol/150 µg levonorgestrel)/7 days 10 µg ethinylestradiol.
- Continuous daily regimen: In 2007 the U.S. Food and Drug Administration (FDA) approved Lybrel (90 µg levonorgestrel/20 µg ethinylestradiol tablets) (WyethAyerst) for a low-dose, continuous, non-cyclic combination oral contraceptive. In clinical trials (n = 2134) performed by the Conrad Programm (US) (2006) a pearl index of 1,26 and in 79 % absence of bleeding has been reported [38]. Nevertheless the high rate of intermenstrual bleedings and a higher pearl index when compared to combined oral contraceptives did not led to a European approval of Lybrel. Ongoing studies are investigating the contraceptive efficacy, the clinical tolerability and the control of the menstrual cycle by a product called Yaz flex, developed by Bayer-Schering-Pharma.
- Extended cycle: An increasing number of women are using OCs as long cycle (3, 6 or more blisters of a continuous combined OC without an OC free interval). Patients must be informed that the extended cycle is an off-label recommendation. Furthermore they have to be informed about the management of break-through bleedings and withdrawal bleedings. If a regular control bleeding occurs, the extended cycle must be stopped and after a pill-free interval a new extended cycle can be started.

In a Cochrane analysis of Edelman et al. [39] oral contraceptives taken continuously for more than 28 days compare favorably to traditional cyclic oral contraceptives. 6 randomized controlled trials met our inclusion criteria. Study findings were similar between 28-day and extended cycles in regard to contraceptive efficacy (i. e., pregnancy rates) and safety profiles. When compliance was reported, no difference between 28-day and extended cycles was found. Participants reported high satisfaction with both dosing regimens, but this was not an outcome universally studied. Overall discontinuation and discontinuation for bleeding problems were not uniformly higher in either group in most studies. The few studies that reported menstrual symptoms found that the extended cycle group fared better in terms of headaches, genital irritation, tiredness, bloating, and menstrual pain. Five out of the six studies found that bleeding patterns were either equivalent between groups or improved with continuous-dosing regimens. Endometrial lining assessments by ultrasound were done in a small number of participants but all endometrial stripe measurements were less than 5 mm.

Nevertheless, there is a great experience in Germany with extended cycles, a

method which is highly accepted by patients and doctors. The use of this regimen in Germany is "off-label" and the patients must be informed.

According to a German study of the Bundeszentrale für gesundheitliche Aufklärung (BZgA) [40] 42 % of all German women prefer regular menstrual bleedings.

Trends

Ethinylestradiol free contraceptives using estradiol or estradiol esters

Over the years, changes made to combined oral contraceptives (OCs) have focused on improving their tolerability by reducing the dose of progestogens and ethinylestradiol (EE), modifying the dosing regimen and incorporating progestogens with more favorable clinical profiles. Additional efforts to improve the acceptability of combined OCs have included the replacement of EE with 17beta-estradiol (E_2). In several historic clinical trials, E_2-containing OCs have been found to provide effective contraception, but their association with unsatisfactory bleeding profiles has largely prevented them from being developed further [41–43], Estradiol valerate (E_2V) is promptly hydrolyzed to E_2 after oral administration, and is identical to E_2 in terms of pharmacodynamics and pharmacokinetics [44]. An OC containing estradiol valerate (E_2V) and dienogest (DNG), an established progestogen that was selected for its strong endometrial effects, in addition to its antiandrogenic properties and lack of androgenic activity [45, 46] has been developed. These properties have enabled E_2V/DNG to be the first E_2-based COC that delivers natural E_2 and provides effective cycle control. E_2V/DNG utilises dynamic dosing in a simple and continuous 1-pill-per-day format, which delivers an estrogen step-down, progestogen step-up regimen over 26 days of active treatment, 2 days of placebo. This regimen was designed to ensure good cycle control by maintaining estrogen dominance in the early part of the cycle and progestogen dominance in the mid-to-late part of the cycle. It also provides stable trough E_2 levels over the whole 28-day cycle, with low variability in E_2 levels over 24 hours [47]. Clinical trial data show that E_2V/DNG effectively inhibits ovulation [42] and offers women an acceptable bleeding profile, with lighter bleedings and a significant reductions in the duration of withdrawal bleeding per cycle compared with EE/LNG [48]. Significantly more patients per cycle experienced absent withdrawal bleeding, although only in a minority of cycles. The efficacy of E_2V/DNG for the treatment of heavy, prolonged and/or frequent menstrual bleeding without organic cause, measured by using the alkaline haematin method, has been investigated in two identically designed double-blind, randomised, placebo-controlled trials in USA/Canada [49] and Europe/Australia [50]. Together, the 2 studies provide the first evidence from rigorous randomised trials that an oral contraceptive is an effective treatment for HMB. Study results revealed a rapid effect of E2V/DNG, with a significant reduction in MBL seen from cycle 2 onwards. E2V/DNG has been available in multiple countries in Europe since May 2009, and is also available outside of Europe and in the USA.

In the near future a new regimen with natural estrogens (estradiol) in combination with nomegestrol acetate (Organon, Schering-Plough now MSD) will be available.

Research

Other targets for oral contraceptives include the development of estrogen-free contraceptives. Clinical trials are ongoing for sprayon contraceptives (Fig. 1).

New patents have been published in relation to progestins with antihistaminic activity, progestins with additional sulfatase-inhibition, androgen receptor modulators, and progesterone receptor modulators.

Furthermore new progestins are tested for contraception (e. g. nomegestrol acetate, nestorone, trimegestone) which can be used for oral contraceptives, vaginal rings, transdermal contraception via patches or gel and for hormone replacement therapy (HRT).

Research focuses on recent endocrine, biochemical, and genetic information that has been derived largely from the identification of newly identified genes expressed in the ovary, and from knowledge gained by the targeted deletion of genes that appear to impact the ovulation process. To prepare for ovulation, the

Figure 1: Spray-on contraceptive. From JRE 2007; 4(6): 337–57. Reprint with permission from "Museum für Verhütung und Schwangerschaftsabbruch", Wien, www.muvs.org.

ovary must undergo a series of closely regulated events; each of them may be targets of new substances suitable for ovulation inhibition. Small follicles must mature to the preovulatory stage, during which the oocyte, granulosa cells, and theca cells acquire specific functional characteristics. Theca cells begin to synthesize increasing amounts of androgens that serve as substrates for the aromatase enzyme in the granulosa cells, granulosa cells acquire the ability to produce estrogens and respond to luteinizing hormone (LH) via the LH receptor and the oocyte becomes competent to undergo meiosis. The sequence of temporal events that occur during ovulation is initiated in a responsive preovulatory follicle by a surge of LH, which impacts both theca and granulosa cells to stimulate cAMP and activate selective protein kinase signalling cascades. These signalling pathways rapidly induce transcription of specific genes, which are expressed transiently prior to follicle rupture. The induced products initiate or alter additional cell signalling cascades, such as protease-driven cascades, which cause follicular rupture and promote follicular remodelling to form a corpus luteum. Remarkably, many events are spatially restricted to specific microenvironments within the follicle or surrounding interstitial compartments to allow successful expulsion of the cumulus-oocyte complex from the ruptured follicle [51].

There is a special interest in leukotriene inhibitors, new inhibitors of inflammatory-like response, prostaglandins [51]. Furthermore folliculogenesis and ovulation can be blocked via specific inhibitors of follicle stimulating hormone

(FSH) secretion, and inhibition of binding of FSH and luteinizing hormone (LH) to receptors; meiose inhibitor factor and inhibitors of meiose-activating compounds, MPF (maturation-promoting factor), OMI (oocyte maturation inhibitor) [52, 53]. Research is ongoing for new OC formulations with addition of cardioprotective agents. In view to minimize the cardiovascular risk, especially for the perimenopausal women new guidelines are necessary to improve the contraceptive safety.

- **Internet Links**
- Guidelines for prescribing combined oral contraceptives. The new studies confirm that low dose combined oral contraceptives carry an extremely low. (http://bmj.bmj journals.com/cgi/content/full/312/7023/121/a)
- Peters MW, Pursley JR, Smith GW. Inhibition of intrafollicular PGE2 synthesis and ovulation following ultrasoundmediated intrafollicular injection of the selective cyclooxygenase2 inhibitor NS398 in cattle. J Anim Sci 2004; 82: 1656–62. (http://jas.fass.org/cgi/content/full/82/6/1656)
- Oral Contraceptive Prescribing: Should Body Weight Influence Choice of Pill? (http://www.contraceptiononline.org/contrareport/article01.cfm?art=261)
- New product review: desogestrel-only pill (Cerazette) (2003) (http://www.ffprhc.org.uk/pdfs/Cerazette%20CEC%20Approved%2029.04.03.pdf)

Once-a-Month Injectables

Update

Different brands of once-a-month injectables are still available in Middle and South America (e. g. Mesigyna/Bayer-Schering-Pharma). Lunelle (25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate given every 28 to 33 days) were approved by the FDA in 2000 but production was stopped due to problems in manufacturing.

In the Cochrane analysis Gallo et al. [54] analysed combination injectable contraceptives and found that combination injectable contraception results in fewer bleeding disruptions and fewer women stopping use for bleeding reasons than progestinonly injectable contraception. Combination injectable contraception is a highly effective, reversible method for preventing pregnancy. More women using combination injectable contraceptives had regular (cyclical) bleeding patterns than those using progestinonly injectables. Also, fewer women using combination injectables stopped using them because of bleeding reasons than progestin-only users. However, combination injectable users were more likely to discontinue for other reasons. While stopping use can be viewed as a measure of acceptability of the method, these results should be considered with caution. Acceptability depends on many factors.

Trends

A selfinjectable (Uniject/PATH) with the same content like Lunelle is currently in development (Fig. 2).

Figure 2: Uniject: the subcutaneous DMPA formulation will be available as a single-use syringe. From JRE 2007; 4(6): 337–57. Reproduced with permission. Copyright Program for Appropriate Technology in Health (PATH). All rights reserved.

Contraceptive Patch

Update

Evra (Ortho-MacNeil), a contraceptive patch releasing 150 µg norelgestromin and 20 µg ethinylestradiol daily, was first approved by the FDA/US in 2001 (Fig. 3). The patch is applied weekly for three consecutive weeks and followed by one week without patch. The FDA approved updated labeling for the Evra contraceptive patch (November 10, 2005) to warn health care providers and patients that this product exposes women to higher levels of estrogen than most birth control pills. Women who use Evra are exposed to about 60 % more total estrogen in their blood than taking a typical birth control pill containing 35 µg of estrogen (FDA Updates Labeling for Ortho Evra Contraceptive Patch 2005).

In a Cochrane analysis Gallo et al. [54] compared the skin patch and vaginal ring versus combined oral contraceptives. Three randomized controlled trials comparing the combination contraceptive patch to a combination oral contraceptive were found. The trials found that the two methods had similar pregnancy rates. One trial found that patch users were more likely than oral contraceptive users to discontinue early from the trial, but a second trial did not find any differences in discontinuation between the groups. Women using the patch reported breast discomfort more often than the women using the oral contraceptive. The remaining commonly reported adverse events were headache, nausea, painful periods, and abdominal pain, and the reports of these adverse events were similar in the two study groups.

Trends

A smaller patch releasing ethinylestradiol and gestodene (brand name: Fidencia/Bayer-Schering-Pharma, Germany) will be available in the next years (Fig. 3).

Vaginal Ring

Update

The vaginal administration of contraceptive steroids allows excellent cycle control at much lower levels of total steroid exposure.

Several vaginal rings have been developed in the past (levonorgestrel ring by the WHO, progesteronereleasing ring by the Population Council).

Finally, until now only the NuvaRing® (MSD) (made of ethylenevinylacetate copolymer, releasing 15 µg ethinylestradiol and 120 µg etonogestrel) is available in most countries of the world and highly accepted (Fig. 4). NuvaRing® is a unique delivery system that releases progestin and estrogen continuously for 3 weeks so that is used just once-a-month. NuvaRing® is easy to insert and to remove and offers hormone delivery that is more stable than a daily pill but just effective as the pill. Despite of the low estrogen level, NuvaRing® offers a stable cyclus from the beginning.

This ring is inserted on any day from day 1 to day 5 of a menstrual cycle for 21 days, thereafter removed for 7 days ring-free period and discarded.

Complete inhibition of ovulation is observed during treatment with this device. Clinical exposure to NuvaRing®

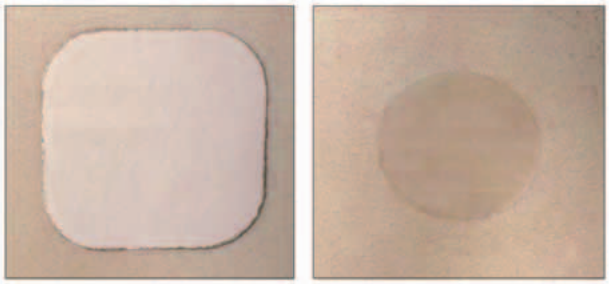

Figure 3: Contraceptive patches: Left: Evra (Ortho-McNeil). Right: Fidencia (Bayer-Schering-Pharma). From JRE 2007; 4 (6): 337–57. Reprint with permission from Bayer-Schering-Pharma

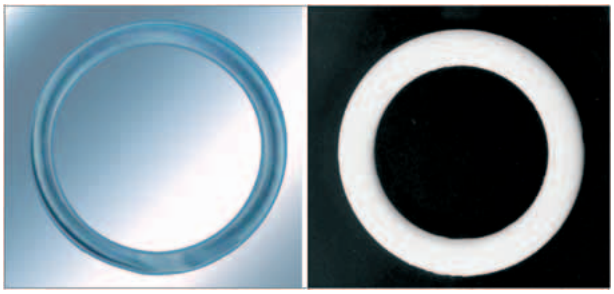

Figure 4: Left: NuvaRing® (Organon). Reprint with permission. Right: Nestorone® vaginal ring. From JRE 2007; 4(6): 337–57. Reprint with permission: photo of Nestorone® Vaginal Ring © 2007, The Population Council, Inc.

for 1786 women-years has resulted in 21 pregnancies, giving a Pearl-Index of 1.18. Withdrawal bleeding (4.7–5.3 days) is regular (97–99 % of cycles) with rare incidence of irregular bleeding (2.6–6.4 %). The cycle control is good with the use of this combined contraceptive vaginal ring. NuvaRing® is well tolerated and accepted by women as compared to oral pill (s. review [55]).

Trends

New vaginal rings containing nomegestrol are under way (special indication: for lactating women).

Clinical trials of a vaginal ring releasing 150 µg of nestorone (NES) and 15 µg of ethinylestradiol (EE) daily over the course of a year were performed by the Population Council (New York/US) and the Department of Reproductive Health and Research of the WHO (through its HRP program) (Fig. 4). Nestorone is a potent, nonandrogenic, 19-norprogesterone derivative, which is not active when given orally, but is highly active when delivered via non-oral delivery systems, such as implants or transdermal preparations. The high potency of nestorone makes it an excellent candidate for use in contraceptive delivery systems designed to be effective for prolonged periods. The NES/EE vaginal ring is a longacting contraceptive device, but, unlike other longterm methods, its use is controlled by the woman without the need for medical intervention.

Other vaginal rings in preclinical and clinical trials releasing contraceptive steroids and/or microbicides are in development. Preclinical studies must show if progesterone, antiprogestins, progesterone receptor modulators, estrogens, antiestrogens, estrogen receptor modulators (SERMS) can be used for transvaginal contraception.

- **Internet Links**
  - Population Council Projects: Vaginal Ring (http://www.popcouncil.org/biomed/femalecontras.html)
  - Safety and Efficacy of a Contraceptive Vaginal Ring Delivering Nestorone® and Ethinyl Estradiol; Study report published by ClinicalTrials.gov (http://clinicaltrials.gov/ct/show/NCT00263341?order=8)

Emergency Contraception

Update

Emergency contraception is using a drug or intrauterine device (IUD) to prevent pregnancy after unprotected sex. This is for backup, not regular contraception.

Postcoital pills are available worldwide, in some countries as over-the-counter pill free of prescription. A onetime use of levonorgestrel (1500 µg in one tablet or in two tablets each containing 750 µg) up to 3 days after unprotected sexual exposure is mostly used. Recently a new emergency contraception pill on the basis of ulipristal acetate has been introduced in the European market which is licensed to be used up to 5 days after unprotected intercourse. The WHO has undertaken research in this area for the past ten years, and our results are helping to improve the safety, efficacy, acceptability, and ease of service delivery of emergency contraceptive methods.

In a Cochrane analysis Cheng et al. [56] analyse interventions for emergency contraception. Levonorgestrel and mifepristone, the latter of which is only registered and available as an emergency contraceptive in China (in doses of 10 mg and 25 mg) and used off label in a limited number of other countries, are very effective with few adverse effects, and are preferred to estrogen and progestogen combined. Levonorgestrel could be used in a single dose (1.5 mg) instead of two split doses (0.75 mg) 12 hours apart. Mifepristone might delay the following menstruation. Women need to be informed about this to avoid anxiety. Another effective method for emergency contraception is the IUD and it can be kept for ongoing contraception.

Trends

There is a special focus on new retrograde contraceptives (emergency contraceptive) which can be used after unprotected intercourse (progestins, antiprogestins, selective progesterone receptor modulators, postcoital insertion of copperbearing T 380A IUD (Paragard).

WHO research is also under way on the use of gestrinone as a possible method of emergency contraception, and other studies are being undertaken on the effectiveness of the IUD for use in emergency contraception. Further initiatives are investigating the possible mechanisms of action of emergency contraceptives.

Selective modulators of progesterone receptors (SPRMs), including antiprogestins and PRMs with partial agonistic activities, look very promising in emergency contraception since they are efficient longer than levonorgestrel (120 h for ulipristal acetate vs 72 h for levonorgestrel). The clinically relevant mode of action of these substances is, like with levonorgestrel, the delay or inhibition of ovulation. The difference is that those substances may be able to be taken later

up until shortly before the LH peak. The SPRM ulipristal has been able to show that it is still efficacious at a time when the LH levels have already started to rise, thus increasing the chance to still intervene at a moment when the risk of conception is at its peak [57]. Clinical trials have demonstrated a significantly improved effect on the prevention of unwanted pregnancies. Ulipristal acetate 30 mg (marketed as ellaOne®) has already reached the European approval and is on the market in Europe. It is expected to reach the US market in 2011 [58].

- **Internet Link**
- WHO information sheet for emergency contraception (http.//www.who.int/reproductivehealth/family_planning/docs/ec_factsheet.pdf)

Inhibition of Fertilisation

Inhibition of fertilisation can be performed by intrauterine devices (inert or drug-loaded IUDs with copper or progestins), depot injectables, implantables, mechanical methods (diaphragm, portio caps), spermicides, behavioural methods, and surgical methods (tubal ligation). Immunocontraception focussing on surface antigens of the oocyte and sperm antigens are in preclinical studies.

Intrauterine Devices (IUD)

Update

The first generation of IUDs consists of inert plastic material. The second generation are medicated IUDs, loaded either with copper or progestins. The most commonly used intrauterine devices (IUDs) (or coils) are made up of a T-shaped or horseshoe-shaped frame surrounded by thin copper wires. The amount of wiring determines the 'dose' of a device.

Copper releasing IUDs: Today, medicated IUDs releasing copper are accepted worldwide (e. g. NovaT, Multiload 375). The primary mechanism of contraceptive action of copper IUDs is believed to be a prefertilization effect, interfering with the passage of sperm through the uterus but there is some evidence suggesting that there could also be a postfertilization effect. Whereas the e. g. Multiload 375 and NovaT can be used up to 5 years other copper IUDs (not available in germany) can be used up to 10 years. The risk of infertility in women not on risk for sexually transmitted disease seems to be low.

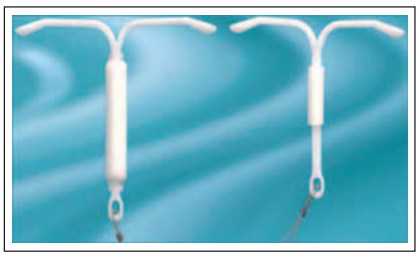

Figure 5: Levonorgestrel-releasing intrauterine systems: Left: Mirena®; Right: "Small Mirena®". From JRE 2007; 4(6): 337–57. Reprint with permission from Bayer-Schering-Pharma

In a Cochrane analysis Kulier et al. [59] showed that devices containing higher dose of copper are more effective in preventing pregnancy over a longer time period (up to 12 years). Those devices may have more side effects, such as bleeding, in the first 2 years, but are similar after that.

Levonorgestrel-releasing system: The Mirena® levonorgestrel-releasing intrauterine system belongs to the group of medicated IUDs releasing levonorgestrel intrauterine over a period of up to 5 years (Fig. 5). Additional non-contraceptive benefits are a lower rate of PID, dysmenorrhoea, lower menstrual blood flow, shorter duration of menstruation, and decrease of bleeding episodes in patients with menorrhagia. Furthermore 20 % of all users will experience an amenorhoea during the first 5 years of Mirena® use, and up to 60 % when using the second Mirena®. The contraceptive effects of Mirena® are based on mainly local actions of levonorgestrel (LNG) in the uterus: thickening of cervical mucus, inhibition of sperm motility and function, and prevention of endometrial growth. In addition, some women experience suppression of ovulation, although after the first year, mos cycles are ovulatory. Based on these mechanisms, Mirena provides high contraceptive reliability: the failure rate of Mirena is approximately 0.2 % at 1 year and a cumulative failure rate of approximately 0.7 % at 5 years. This contraceptive efficacy is comparable to that of female sterilization, with full reversibility of fertility upon removal.

In addition to its contraceptive action, Mirena® also leads to a significant reduction in both the amount and duration of menstrual bleeding, and alleviates menorrhagia/heavy menstrual bleeding (HMB) and dysmenorrhea. The efficacy of Mirena in the treatment of HMB has been compared to both other medications and to surgery: Mirena is superior to conventional medical therapy in the treatment of HMB, and is therefore recommended as the firstline treatment for HMB by international guidelines [60]. The efficacy of Mirena is similar to that of endometrial ablation, as confirmed by a recent metaanalysis [61]. Compared to hysterectomy, treatment with Mirena results in equal improvement of health-related quality of life, even in long-term studies [62].

Due to its strong, localized progestogenic effect on the endometrium, Mirena® has also been studied for prevention of endometrial hyperplasia during ERT in peri- and post-menopausal women, and Mirena® is approved for this indication in many countries.

The initial months of use of Mirena® are associated with irregular bleeding and spotting, which is followed by reduction of menstrual bleeding and oligo-amenorrhea. The initial irregular bleeding/spotting should be always taken into account in patient councelling, to avoid unnecessary removals.

Frameless IUDs: The frameless copper-releasing GyneFix is still not widely used. In a Cochrane analysis O'Brien and Marfleet [63] compared frameless versus classical intrauterine devices for contraception. The frameless IUD performs similarly to traditional IUDs but does not reduce bleeding and pain associated with standard IUDs. Traditional intrauterine devices (IUD) with plastic frames have side effects such as excessive bleeding and pain that were thought to be due to the frame. This review found that symptoms of bleeding and pain, and contraceptive efficacy were not improved with the frameless device. Trials are needed to see if the frameless IUDs could benefit women who have not had children.

Trends

New intrauterine devices under development are: Swing: copper-releasing with coil stem; IUD releasing a progesterone receptor modulator (CDB2914); Copper

Figure 6: New diaphragms and cervical caps. From JRE 2007; 4(6): 337–57. Upper row: SILCS (left). Reproduced with permission. Copyright Program for Appropriate Technology in Health (PATH). All rights reserved. Lea's Shield (right); reprint with permission. Lower row: FemCap (left); reprint with permission. Oves (right); reprint with permission © 2007 Ibis Reproductive Health, Courtesy of Photoshare.

IUD releasing indomethacin or other prostaglandin synthetase blockers or inhibitors [1].

A smaller Mirena® intrauterine system releasing LNG for a period of up to 3 years is under way by Bayer-Schering-Pharma, Germany (Fig. 5).

A new frameless progestin-releasing IUS is also under way.

The use of antiprogestin in steroid-releasing intrauterine systems cannot yet be evaluated.

Barrier Methods

Update

Diaphragms and portio caps must be used in combination with spermicides. The cervical cap has a use effectiveness of about 82 % for nulliparous women and 64 % for parous women, whereas the method effectiveness is about 91 % and 82 % for nulliparous and parous women, respectively.

Diaphragm: The diaphragm is a thin rubber dome with a springy and flexible rim. It is inserted into the vagina, fits over the cervix and is held in place by vaginal muscles. A diaphragm holds spermicide in place over the cervix. After intercourse, it should be left in place for 6–8 hours. Diaphragms are 86–94 % effective as birth control. Getting a diaphragm requires a fitting in a clinic. During the fitting, a fitting ring is inserted into the vagina. The largest ring that fits comfortably is usually the one chosen. Diagphragms can be inserted up to 2 hours before sex because spermicide in only effective for 2 hours.

Different types of latex diaphragms are available (Allflex Arcing Spring, Reflexions Flat Spring, Ortho Coil Spring in different sizes from 55 to 95 mm in 5 mm steps, Practice Diaphragm). Furthermore there are nonlatex diaphragms such as Milex Silicone Diaphragm Omniflex, Milex Silicone Diaphragm Arcing Style in sizes from 60 to 90 mm in 5 mm steps. A Cochrane analysis [64] found that there is not enough evidence about the effects of using a diaphragm without a spermicide, but it may increase unwanted pregnancies.

SILCS (silicone device placed in the vagina to cover the cervix), a new diaphragm is in development: It has "grip dimples" on the sides of the rim, and its shape makes insertion and removal easy (Fig. 6).

Cervical caps: The cervical cap is a cervical barrier type of birth control. It fits snugly over the cervix and blocks sperm from entering the female reproductive tract. Cervical caps may be made out of latex or silicone.

Dumas: Rubber/latex, sizes 1, 2, 3, 4, 5

Vimule: Rubber/latex, sizes 1, 2, 3

Lea's Shield (Canadian brand; in US: Lea Contraceptive, in Europe: LEA contraceptivum) is a female barrier method of contraception, reusable, made of medicalgrade silicone, inserted in the vagina over the cervix with the intention to block sperm. It is used in conjunction with spermicide. Lea's Shield most strongly differs from other female barrier methods such as the cervical cap and diaphragm because it exists only in one size (does not need to be specifically fitted to each woman). It stays in place because of suction and it has a valve (creation of suction, passage of cervical fluids) (Fig. 6).

The **Prentif Cervical Cap** (Rubber/latex, sizes 22, 25, 28, 31 mm). was a popular cervical cap which is no longer available in the US but its still in use in other countries (e. g. UK).

The **Oves Cervical Cap** is a disposable cap, made of hypoallergenic silicone which can be worn up to 72 h (Fig. 6).

A new model is the **FemCap** made of a nonallergenic, durable silicone material, coming in three sizes. The FemCap is placed over the cervix and is partially filled with contraceptive jelly or cream (Fig. 6).

In a Cochrane analysis Gallo et al. [65] found that the Prentif Cap worked as well as the diaphragm to prevent pregnancy. The FemCap did not prevent pregnancy as well as the diaphragm. Both cervical caps appear to be medically safe.

Trends

New cervical caps on the market make removal easier compared to older models.

Hormonal Implants (Tab. 1)

Update

An implant is a small flexible rod or a capsule placed just under the skin in the upper arm. The Population Council, a nonprofit organization located in New York, began researching subdermal contraceptive implants in 1966. Progestational agents include megestrol acetate, norethindrone, norgestrinone, and levonorgestrel. The Food and Drug Administration (FDA) approved subdermal contraceptive implants delivering levonorgestrel in 1990.

Norplant: The 6-capsule Norplant releasing levonorgestrel was withdrawn from the market in 2002.

Jadelle: Jadelle contains two flexible, silicone-based polymer rods that are

Table 1: Implantables

Progestin	Trade name	Unit	Duration of action
Levonorgestrel*	Norplant	6 capsules	5 years
Levonorgestrel	Jedelle	2 rods	5 years
Etonogestrel	Implanon	1 rods	3 years
Nestrone	Elcometrine	1 capsule	6 months
Nestrone	Elcometrine	1 rod	2 years
Norgestrel	Unilant or Surplant	1 rod	1 year

*) Norplant distribution in the United States ended in 2002

43 mm in length and 2.5 mm in diameter; each rod contains 75 mg levonorgestrel, low levels of which are continuously released into the blood over Jadelle's period of use, approved by the U. S. Food and Drug Administration (FDA) for up to 5 years.

Implanon: Implanon is a non-biodegradable, longacting, progestagen-only contraceptive implant inserted subdermally. The implant is a single rod of 4 cm length and 2 mm in diameter and contains 68 mg etonogestrel (ENG) dispersed in a matrix of ethylene vinyl acetate (EVA) copolymer. The indicated period of use is 3 years. The ENG dose released by Implanon is equivalent to 6070 µg/day shortly after insertion and decreases to about 40 µg/day at the start of the second year, and to about 2530 µg/day at the end of the 3rd year.

– Contraceptive Efficacy: Pearl-Index: 0,04–0,08. The contraceptive efficacy is mainly based on ovulation inhibition [66, 67]. Within 8 hours after subdermal implantation the serum levels of etonogestrel reach values sufficient for ovulation inhibition [67, 68]. An additional contraceptive effect is based on increased viscosity of the cervical mucus [66].

Drug interactions can occur in view to an induction of microsomal enzymes, especially cytochrom-P 450-isoenzyme which leads to a increased metabolism of steroid hormones [69, 70].

– Side effects: Type and incidence of side effects are similar to other progestin only contraceptives. The most important side effects are bleeding disorders, vaginitis, acne vulgaris, breast pain, head ache, weight increase, mood changes and abdominal pain [71–74].

Note: Incident data especially come from observation of full three years of use, whereas the typical observation period for e. g. a new COC is one year in the phase 3 studies. Incidence data should thus be seen in perspective of this much longer observation period and not be seen as higher than COCs.

The impact on bone density has been analysed in two clinical studies. In a 2year trial enrolling a total of 73 healthy women Beerthuizen could not find significant changes in bone density at the lumbal spine, the proximal femur as well as distal radius between Implanon® users and IUD users. It has been concluded that by maintenance of the endogenous FSH and E_2 levels in Implanon users occur no estrogen deficiency symptoms and subsequent no bone loss [75]. In contrast, Bahamondes found in a study enclosing 111 women, conducting a bone density measurement before and 18 months after insertion of a etonogestrel or a levonorgestrel containing implant, a slight but significant change at the middle part of the ulna whereas the distal radius remainded unchanged [76].

In summary, the CHMP agreed that there is at this time no firm evidence of an association between Implanon exposure and an increased risk of breast cancer in young women.

– Breast Feeding Women: Implanon® seems to have no impact on the quality and quantitiy of the milk of breastfeeding women and no impact on the development of the child [77–79]. It can be used during the breast feeding period. The growth and development of the child should be carefully observed.
– Insertion and Removal: The implantation and removal of Implanon® should be exclusively done by a physician skilled in this technique. The implantation should be done at the inner part of the upper arm approximately 8–10 cm above the medial epicondylus of the humerus. In right hander patients the left arm should be preferred. After the correct insertion Implanon® can be immediately and during the complete period localized by palpation. If it is no palpable a localization can be done with high frequence ultrasound using ultrasound heads with high resolution or computer tomography [80–82]. In single cases a small operation with an incision of up to 1 cm might be necessary. Already one week after removal of the implant, etonogestrel is not detectable anymore in the serum [68]. After the removal of Implanon® ovulation as well as fertility occur fast [66, 67, 83].

Summary: The main benefit of any contraceptive method is efficacy and the CHMP considered that Implanon shows excellent efficacy with no evidence of decline neither during the 3rd year of use nor in heavy women.

In Germany there is a special official recommendation to use Implanon® only after intensive counselling of the patient and information about the possible risk associated with Implanon® removal [84].

(Author's comment: Traning in insertion and removal is essential. If you are experienced in Implanon insertion and do it correct subdermally, you will have no problem with removal) (see also [85]).

In total, about 5 million Implanon implants have been sold worldwide up to July 2008.

Implanon NXT: A new radiopaque Implanon NXT (2× 40 mm), which can be easily located, using xray, will be available worldwide 2010 by MSD. The core of the implant consists of 37 % ethylene vinyl acetate as copolymer, 60 % etonogestrel (68 mg) and 3 % barium sulfate. In addition the inserter has been improved leading to an insertion of the implant in the subdermal tissue not deeper than 4 mm (Fig. 7).

In a Cochrane analysis Power et al. [86] found, that all the trials identified compared different types of contraceptive

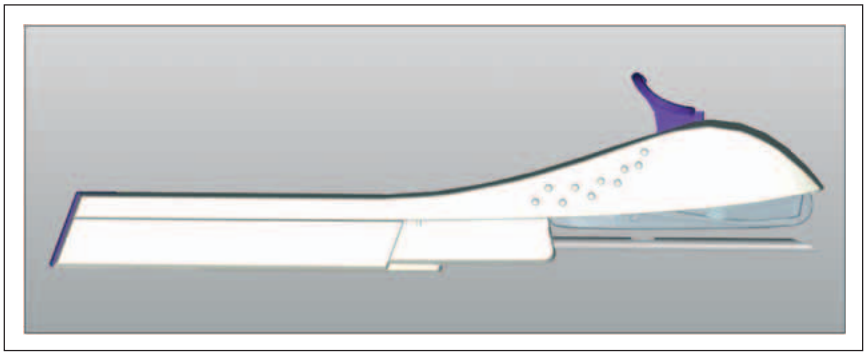

Figure 7: Implanon NXT (due to the content of barium sulfate it can be easily located by x-ray). Reprint with permission from MSD.

implant. No trials were found that compared implants to other contraceptive methods. All the implants were highly effective methods of contraception in the selected women. The majority of women using contraceptive implants chose to continue with the method long term, over 80 % of women were still using their implant at two years. Women in developed country studies were less likely to continue with these methods when compared to women in developing country studies. The most common reported side effect was of irregular vaginal bleeding. Bleeding with all implants became less frequent with time. Removal was quicker for Implanon and Jadelle than for Norplant. Insertion problems were rare with any of the implants. Problems at removal were uncommon but were significantly more likely to occur in Norplant users than Implanon users. Comment: This analysis needs to be updated.

Trends

The following contraceptive implants are in development: Elcometrine consists of 1 capsule with nestrone acting over 6 months; Elcometrine using 1 rod with nestrone and an efficacy over 2 years and Uniplant or Surplant with 1 rod containing norgestrel over 1 year. New biodegradable implants (capsules or rods) and implants with new steroids have been under investigation for years.

Depot Injectables

Update

In 1992, the FDA approved depot medroxyprogesterone acetate (DMPA) as a long-acting, injectable progestational contraceptive. DepoProvera is medroxyprogesterone acetate aqueous suspension 150 mg in 1 ml which must be administered every 3 months. Noristerat is norethisterone enantate 200 mg in 1 ml in an oily liquid which provides effective contraception for 2 months. Furthermore, there is a high incidence of amenorrhoea (50 % after one and 75 % after two years). Migraine and headache are also common.

With regard to bone metabolism:

- There should be no restriction on the use of DMPA, including no restriction on duration of use, among women aged 18–45 years who are otherwise eligible to use the method.
- Among adolescents (menarche to < 18) and women over 45 years, the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk. Since data are insufficient to determine if this is the case with long-term use among these age groups, the overall risks and benefits for continuing use of the method should be reconsidered over time with the individual user.
- Recommendations regarding DMPA use also pertain to use of NETEN.
- There should be no restriction on the use of other progestogen-only contraceptive methods among women who are otherwise eligible to use these methods, including no restrictions on duration of use.
- There should be no restriction on the use of combined hormonal contraceptive methods among women who are otherwise eligible to use these methods, including no restrictions on duration of use [87].

In a Cochrane analysis, Draper et al. [88] compared depot medroxyprogesterone versus norethisterone enanthate for long-acting progestogenic contraception. In summary, therefore, data from the trials included in this review indicate little difference between the effects of these methods, except that women on DMPA are more likely to experience cessation of vaginal bleeding during its use. There was inadequate data to detect differences in some non-menstrual clinical effects, and considering that this contraceptive method remains in use in some countries, further research is indicated.

DeposubQ provera 104™: A new three-month injectable (Sayana) containing low dose depot medroxyprogesterone acetate (104 mg) has been recently introduced by Pfizer. DeposubQ provera 104™ (deposubQ) is a new formulation of the injectable contraceptive DepoProvera®. Administered through subcutaneous injection, deposubQ contains 30 % less depot medroxyprogesterone acetate (DMPA) than the intramuscular presentation (DMPA IM, 150 mg/ml medoxyprogesterone acetate sterile aqueous suspension) while providing equivalent efficacy and safety. DeposubQ is indicated for the prevention of pregnancy in women of childbearing potential and for management of endometriosis-associated pain *(Author's comment: not yet in Germany).*

DeposubQ provera 104 mg/0.65 ml contains medroxyprogesterone acetate (MPA), a derivative of progesterone, as its active ingredient. When deposubQ is administered to women every 3 months (12–14 weeks), it inhibits the secretion of gonadotropins, preventing follicular maturation and ovulation and causing endometrial thinning. Because DMPA is absorbed more slowly when administered subcutaneously, a 30 % lower dose of deposubQ in comparison with DMPA IM allows for a lower peak MPA concentration and aboveminimum serum MPA levels for suppressed ovulation over a targeted 3 months [89].

- Effectiveness: As the following clinical evidence suggests, deposubQ provides equivalent efficacy, safety, and immediacy of onset to that of DMPA IM and effectively suppresses ovulation for at least 13 weeks regardless of race, ethnicity, or body mass index (clinical studies have been performed between body mass index 18.2 and 46.0 kg/m^2).
- Pearl-Index: In 2 Phase-III-Studies with a total of 2045 users (18–49 years, at least 20,000 cycles) after one year no case of unintended preg-

nancy occurred. This corresponds to a pearl-index of 0.

– Pharmacokinetic: After subcutaneous injection of 104 mg MPA within 24 hours the contraceptive serum level of MPA (> 0.2 ng/ml) is achieved which remains at least for 13 weeks.
– Contraindications and side effects: DeposubQ is expected to have equivalent, if not improved, tolerability in comparison with the DMPA IM formulation because side effects are generally dose-dependent [90]. Contraindications are identical to those of DMPA IM, and common side effects for both deposubQ and DMPA IM include headache; bleeding irregularities (including amenorrhea, irregular spotting or bleeding, prolonged spotting or bleeding, and heavy bleeding irregular bleeding typically decreases over time, and amenorrhea becomes more common); increased weight; and injection site reactions typically mild injectionsite pain, granuloma or atrophy. While use of DMPA IM and deposubQ is associated with decreased bone mineral density, no evidence suggests that use of DMPA leads to significantly increased risk of bone fracture [91]. Bone loss associated with DMPA use is reversible, and prior use of DMPA is not likely to be an important risk factor for low bone density or fracture in older women many years after discontinuation [92].

Trends

See also once-a-month injectable.

Several progestin-only injectables are in use or under investigation in various countries. Injectables using microspheres or microcapsules containing one or more hormones also are under investigation. A sterile solution suspends the time-released spheres. The microsphere contains a polymer commonly used in a biodegradable suture, polydllactidecoglycolide. Depending upon the formulation, injectable microspheres provide contraception for 1, 3 or 6 months. Menstrual disturbances are the primary side effect.

Further improvements as mentioned by the WHO (according to [1] are based on:

- Improved pharmacokinetic profile
  – Biodegradable microspheres: norethisterone, norgestimate, progesterone
  – Controlled particle size distribution: depot medroxy progesteroneacetate (DMPA), levonorgestrel butanoate
- Decreased side effects
  – Monolithic macrocrystals: progesterone, 17-beta-estradiol, testosterone combined for once-a-month administration
- Safer delivery system
- Provision of cyclofem in non-reusable disposable syringes (Uniject, Soloshot).

Natural Family Planning

Update

Recently, interest in natural family planning methods has seen a modest resurgence. Based on fertility awareness, women are able to identify the fertile window as well as peak fertility in their cycle without much effort. NFP methods include avoiding sexual intercourse (or use a barrier contraceptive, like a condom) on the fertile days. The Symptothermal Method (STM) combines the observation of the periovulatory temperature rise and cervical mucus changes and determines the onset as well as the end of the fertile phase according to the doublecheck principle.

Grimes et al. [93] published a Cochrane analysis on the randomized controlled trials that compared NFPmethods. Two trials were found, one from Colombia and one from Los Angeles, California. Both revealed poor research methods and must be regarded as having failed. In contrast, certain (mainly European) variations of the symptothermal method have turned out to be highly effective: Actual data on prospective observational studies found a method-effectiveness of 0.4 pregnancies per 100 women years, provided the appropriate guidelines are consistently adhered to [94, 95]. Therefore, these methods belong to the most effective methods of family planning and may also be an option for patients at risk.

There are two new methods which are less effective and actually recommended for developing countries: The standard day method is based on abstinence/protection from cycle days 8 to19. The "two day" method is based on cervical mucus observation.

Today, fertility awareness based methods are a good choice for women or couples seeking a safe and healthy method at low cost. Disadvantages include the necessity of a learning phase and the challenge of sexual behaviour.

Besides contraception, NFP can also be integrated into the management of subfertility and is an interesting contribution to gynaecological endocrinology: long-term cycle monitoring may support medical diagnosis and therapy. For all applications, effective use depends on good instruction of the women.

Cycle monitors promise to detect the fertile and infertile days by using different markers of fertility in a woman's menstrual cycle. Actually, there are different computer thermometers (e. g. Cyclotest®, Babycomp®, Bioself®) and hormonal gadgets (e. g. Persona®, Ovarian Monitor®) available. They are quite interesting, but are less effective than the STM (medium efficacy) [96].

Trends

Fancy monitoring devices for follicular maturation and ovulation failed to show a benefit for contraception and most of them have been offered for cycle monitoring in infertile patients.

Spermicides

Update

Spermicides are chemical products inserted in a woman's vagina before sex that inactivate or kill sperm. They have been available for more than 40 years, and the rigorous contraceptive testing required today by the U.S. Food and Drug Administration was not required at the time of their approval. The main chemicals used in spermicides are nonoxynol-9, octoxynol-9, menfegol, and benzalkonium chloride. Of these, nonoxynol-9 is the most common. Research on the effectiveness of spermicides, particularly nonoxynol-9 (N-9), to reduce transmission of sexually transmitted diseases has provided conflicting results. A recent statement from the Medical Advisory Panel of the International Planned Parenthood Federation recommends that N-9 should be used only in combination with a female mechanical barrier method and that condoms prelubricated with N-9 have no advantage in contraceptive efficacy and should no longer be recommended.

Spermicides can be bought over the counter from the chemist or pharmacist. They are available as creams or gels. The active ingredients include nonoxynol-9 and octoxinol.

Trends
Spermicides with antimicrobiotic activity are under way to provide additional protection against HIV and other sexually transmitted diseases.

Microbicides with contraceptive action (according to [1]:
- Products that create a protective physical barrier in the vagina: e. g. sulfated and sulfonated polymers, such as cellulose sulfate, polystyrene sulfonate.
- Products which increase vaginal defense mechanisms by maintaining natural acidity (which immobilises sperm): e. g. BufferGel and Acidform.
- Surfactant products: e. g. acylcarnitine analogs, C31G.
- Products which block attachment of HIV to target cells and spermzona pellucida fusion: e. g. naphthyl urea derivatives.

Algae gel against HIV: New gel derived from algae are in clinical trials in view to a possible HIV protection. In preliminary lab tests they say it proved to be 95 % efficient. The inventor hopes the gel – one of a new generation of microbicides seen as key to prevent HIV infection in women – will be on the market in 7 years (http://news.bbc.co.uk /2/ hi/health/6266527.stm).

Cellulose sulfate gel against HIV: A WHO trial in South Africa and India testing an anti HIV gel containing cellulose sulfate has been recently stopped.

„Molecular condom“: ‘Smart’ vaginal drug delivery system (DDS), called a ‘molecular condom’. It is composed of a biologically responsive polymer that is a liquid at room temperature (for improved coating of tissue) and gels when it comes in contact with tissue at body temperature (for improved retention). The gel system is pH sensitive so that when the molecular condom comes in contact with semen it liquefies and releases entrapped antivirals into semen in a burst profile (http://www.bioen.utah.edu/faculty/pfk/pages/projects_3.htm)“. However, the technology, featured in the Journal of Pharmaceutical Sciences, is still around five years away from being tested in humans.

- **Internet Links**
- Microbicides: STD protection with or without contraception (http://www.csa.com/discoveryguides/micro/overview.php?SID=9jlmaiv73hts256smm41b5uou2)
- Contraceptive methods: Spermicides (http://www.rho.org/html/contspermicides.html)

Vaginal sponges
Update
Natural sea sponges soaked in spermicide and inserted in the vagina before intercourse have been used throughout history for contraception. In the past decade, several companies have worked to update and reintroduce this method. The sponge creates a physical barrier between the semen and the cervix and traps the sperm in the sponge. It also acts as a chemical barrier by releasing spermicide. Three contraceptive sponges are currently available in some countries. The sponge provides between 12 and 24 hours of protection, depending on the brand used.

Protectaid: The new Protectaid® contraceptive sponge is a unique barrier contraceptive device made of polyurethane foam impregnated with F5 Gel®. The individually wrapped sponge is ready to use and is designed with diecut slots for easy insertion and removal.

The **Today Sponge** is a small polyurethane foam sponge containing 1 g of nonoxynol-9 (N-9). It is a one-size, over-the-counter product and can be worn for 24 hours. It was approved by the FDA in 1983 for sale in the United States. In 1994, the manufacturer halted production of the device because of production problems. The product line was bought by Allendale Pharmaceuticals in 1995, who has been trying to reintroduce production for the U.S. market. In June 2005 the Today Sponge returned to stores in the United States. The Today Sponge is also available in Canada.

Female Condom
Update
The female condom is a sheath made of thin, transparent, soft plastic that a woman inserts in her vagina before sex. It has two rings: a flexible removable ring at the closed end to aid with insertion, and a larger flexible ring that remains outside the vagina at the open end to help protect the external genitalia. Since its introduction in the early 1990s, the female condom has become an important option to assist some women in protecting themselves and their partners from unwanted pregnancies and sexually transmitted infections. The only currently available female condom is the soft, transparent, polyurethane sheath inserted in the vagina before sex. Although the device is marketed and approved as a single-use-only device, reuse by women who are not able to access a new female condom has been reported in a number of countries. The female condom is four times more expensive than male condoms.

New female condoms under way according to the WHO [1] are: polyurethane female condoms (PATH), female condoms made of natural latex (Reddy, other) or plastic material.

Femidom (made of polyurethrane) is avaiblabe since several years. FC2 (made of nitrile), V-Amour (made of latex) are the names of the new products on the market.

Female Sterilisation
Update
Sterilisation (female and male) is still the most widely used method of fertility regulation in the world. It is estimated that 187 million couples rely on female sterilisation worldwide, and a further 42 million rely on male sterilisation (WHO Research on Reproductive Health 2000–2001). The highest prevalence of female sterilisation in the world is in Puerto Rico (49 % of women of reproductive age who were ever in a union are sterilized) [97].

For many women in developing countries, sterilisation is the first-choice method of contraception that they use. Tubal sterilisation is the most common method of contraception used in the United States. More than 10 million women in the United States are sterilised. The Centers for Disease Control and Prevention reported cumulative pregnancy rates for surgical sterilisation in the United States of 5.5 pregnancies/1000 women at 1 year, 13/1000 at 5 years, and 18.5/1000 at 10 years. That is, there

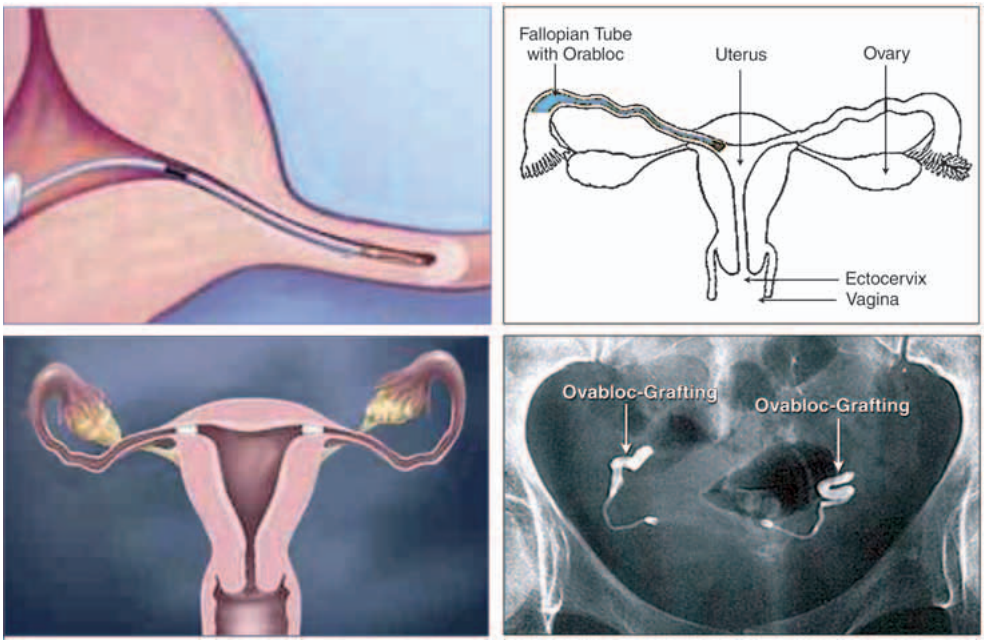

Figure 8: New female sterilisation techniques. From JRE 2007; 4(6): 337–57. Left: Upper figure: Essure; reprint with permission from Conceptus Inc. Lower figure: Adiana. Source: www.thewelltimedperiod.blogspot.com; reprint with permission. Right: Ovabloc. Source: www.ovabloc.com/ovabloc-de/eingriff.html; reprint with permission from aap bio implants group.

were almost two pregnancies per 100 women by 10 years, though this risk varied by method and timing of sterilization, age, race, and ethnicity [85].

Tubal ligation or sterilisation (tying the tubes) is a common method of fertility regulation. It is usually done by using the following methods: mini-laparotomy (through a small cut in the abdomen), laparoscopy ("keyhole" surgery through a tube inserted through the umbilicus (belly button) or a very small cut), or culdoscopy (using a tube, but through the vagina) [98].

In a Cochrane analysis, Nardin et al. [98] analysed the techniques for the interruption of tubal patency for female sterilisation. Effective techniques for tubal sterilisation (blocking the fallopian tubes) include cutting, tying, clips, rings and electric current, but their comparative effectiveness is not clear. The review of trials found that all techniques are effective in preventing pregnancy, with few adverse effects. There is too little evidence to which technique is most effective. Pregnancy after tubal sterilisation is less likely if an experienced practitioner has performed the procedure.

In another Cochrane analysis, Kulier et al. [99] analysed mini-laparotomy and endoscopic techniques for tubal sterilisation. The review found that overall, laparoscopy had fewer complications than mini-laparotomy, but it requires more sophisticated expensive equipment and greater skills. Culdoscopy has higher rates of complications.

Quinacrine: Since more than 20 years a chemical sterilisation with Quinacrine is evaluated in clinical triats: Occlusion of the fallopian tube by introduction of the polymerising agent Quinacrine.

New techniques for female sterilization are:

Essure: Hysteroscopic sterilisation by insertion of titanium in the proximal part of the fallopian tube (Fig. 8). Essure is not available in family planning programs in developing countries, nor is it likely to become available, because of considerations of cost, practicality, and (the lack of) comparative advantage [85].

Adiana: Heating the inner lining of the fallopian tube by radiofrequency and insertion of a soft, inert polymer matrix via a delivery catheter (Fig. 8).

Ovabloc: Sterilisation method for women whereby a rubber plug is inserted into both fallopian tubes (Fig. 8).

Trends
Improvement of endoscopic techniques for surgical sterilisation. Decreasing number of female sterilisations in developed countries due to a high acceptance rate of the levonorgestrel IUS (Mirena) which offers additional non-contraceptive benefits whilst providing the same efficacy in contraceptive reliability.

- **Internet Links:**
  - Bulletin of the World Health Organization. Bull World Health Organ 81(2) Geneva 2003 (http://www.scielosp.org/scielo.php?pid=S00429686200300020013&script=sci_arttext)
  - Reproductivehealth/Unintended Pregnancy/Sterilization (http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Sterilization.htm)

Immunocontraception
Update
Immunocontraception is a non-hormonal, nonsteroidal method of contraception. Various targets have been discussed. Oocyte antigens, sperm antigens, immunisation against GnRH etc.

Oocyte antigens: One target for immunocontraception are the surface antigens (ZP1, ZP2, ZP3) of the oocyte which play a role in sperm attachment and penetration, based on the use of porcine zona pellucida (pZP) proteins. In animals, pZP vaccine creates an immunological response. An antibody layer forms around the egg cell which binds to and blocks the sperm receptor sites, thus preventing penetration of the sperm cell and successful fertilisation. Blocking of all

sperm receptor sites relies on antibody concentrations that are sufficiently high to achieve this and should the concentrations fall below a critical level, which happens over time, the cow will once again be fertile. pZP only targets the zona pellucida of the female animal and has no direct effect on behaviour. Because the animal does not fall pregnant she will continue to show an oestrous.

Spermatocyte antigens: Fertilisation-related antigens at the surface of spermatozoa are also a target for immunocontraception. While there are several lines of evidence pointing to the possibility of inducing immunity to sperm, in practice many roadblocks have appeared such as sperm antigens that cross-react with other somatic antigens, effective sperm antigens that do not affect fertility, short-acting immunity, and the problems of producing high titers in the local environment of the genital tract. The female genital tract is not rich in lymph tissue but IgG and IgA antibodies do occur there, probably originating from gut-associated lymphoid tissue. Not only is a very high titer of antibodies needed to block fertilization in vivo but local immunization is ineffective in inducing high titers. Probably combined local and systemic routes will be required. Several sperm antigens such as lactate dehydrogenase C4, PH-20, sperm protein (SP)-10, fertilization antigen (FA)-1, FA-2, cleavage signal (CS)-1, NZ-1, and NZ-2 have been proposed as potential candidates for vaccine development [100].

Trends
The possible hazards of immunocontraception are cross-reactions of the antibody of non-reproductive tissue, unpredictable titers of antibody leading to a prolonged sterilisation, and other safety issues. Immunocontraception is gaining more and more importance in animal contraception (e. g. rabbits, deer etc.).

Antiprogestins
Antiprogestins for contraception can be used according to the WHO in different regimens [1]:

- Sequential regimens:
  - Mifepristone + Norethisterone
  - Mifepristone + Medroxyprogesterone acetate
  - Mifepristone (days 1–15) + Nomegestrol acetate (days 16–28)
- Continuous regimen:
  - Mifepristone 0.1–10 mg/day
- Weekly use:
  - Mifepristone 2.5–50 mg doses
- Monthly use:
  - Mifepristone 200 mg 2 days after the LH peak
- Emergency contraception:
  - Mifepristone 10 mg

The use of progesterone receptor modulators for postcoital contraception based on inhibition of follicular growth and ovulation inhibition has been discussed in the chapter on emergency contraception.

Implantation Inhibition

Immunocontraception
Immunocontraception is focussing on inhibition of implantation of the early embryo development. The method developed by WHO is based on, and directed against, human chorionic gonadotropin (hCG), a hormone produced by the early embryo within a few days after fertilization and which is necessary for the maintenance of pregnancy. As the result of a large number of studies comparing a variety of preparations, a novel, slow-release formulation of the hCG immunocontraceptive has been selected for clinical evaluation. This preparation offers the promise of providing 6 months or more of protection against pregnancy following a single injection, without producing side effects that would make it unacceptable for use. The preparation has been evaluated for safety and potency in preclinical studies in animals and an application has been made to the drug-regulatory authorities to carry out a dose-ranging, Phase-I clinical trial with this preparation in women volunteers.

Also promising are the female genes and proteins responsible for sperm-egg fusion:

Zygote arrest 1 (ZAR1) gene plays a central role in the fusion of the sperm and egg pronuclei, the nuclei containing genetic matter.

Bin1b binds to the heads of sperm, inducing sperm motility. Blocking the action of this molecule could have a contraceptive effect because sperm would not be able to reach or penetrate the egg.

- **Internet Links**
  - Population Reports (2005): Novel, GeneBased Approaches Promise Dramatic Change in Contraception (http://www.infoforhealth.org/pr/m19/supplements/novel.shtml)

Anti-Implantation Agents
Anti-implantation agents are intended to be taken on only one occasion during the menstrual cycle. They could be used regularly as a once-a-month method or less frequently on an "as-needed" basis in the absence of regular contraception, or as a back-up method in the event of suspected failure of a regular contraceptive method. They could be free of the logistical problems associated with the provision and use of some other family planning methods, they could also have fewer side effects, and their infrequent use would make them relatively inexpensive.

A collaborative initiative on basic research in implantation between the Rockefeller Foundation and HRP was established in 1998 to help in the development of such a method, which is still at an early stage.

Summary

The variety of contraceptive methods available today spans a broad spectrum, and to help facilitate the selection process. Physicians need to be aware of the characteristics of each option. An informed physician can help patients make the best choice for their particular medical, social, and philosophical requirements or preferences.

However, existing methods of contraception are not perfect, and their acceptability is limited by side effects and inconvenience. Even in developed countries where contraception is freely available, many unplanned pregnancies occur. There is thus a real need for new methods of contraception to be developed that are more effective, easier to use, and safer than existing methods.

Predicted Developments (modified according to [1, 101]):

Within 5 years: New delivery systems of conventional contraceptives such as vaginal rings, transdermal patches, and

gels. Contraceptives that also protect against sexually transmitted disease. Furthermore new oral contraceptives with new progestins in combination with estradiol or estradiol-esters.

Short term (< 10 years): „Once-a-month" pill that inhibits implantation; antiprogestogens used for an estrogen-free contraception (note: use limited to potential of misuse!); orally active, non-peptide antagonists of gonadotropin-releasing hormone for men and women; new contraceptive substances (e. g. progestin, antiprogestin, progesterone receptor modulator, estrogen receptor modulator) releasing intrauterine system.

Long term (> 10 years): Antagonists of follicle-stimulating hormone receptor; arrest of spermatogenesis or sperm maturation; arrest of final maturation of oocyte, such as with phosphodiesterase inhibitors; inhibitors of follicle rupture.

Possible targets for new contraceptives are (according to [1]
- Gametogenesis
- Sperm motility
- Sperm capacitation
- Acrosomal reaction
- Follicular development
- Implantation

Some of the more promising developments according to a recent release of the WHO [1] are:
- Lonidamine analogues: deplete immature germ cells from seminiferous epithelium
- Inhibitors of epididymal proteins: eppin (a male specific spermbinding protein containing protease inhibitor consensus sequences) and cystatin-11 (a novel member of the CST type 2 family of cysteine protease inhibitors)
- Inhibitors of testis-specific enzymes: GST (glutathione S-transferase) and SAC (soluble adenylate cyclase)
- Inhibitors of fusion of sperm with zona pellucida
- Change in endometrial receptivity: LIF antagonists; antibodies against LIF, IL-11 or the IL-11 receptor; ebaf (endometrial bleeding-associated factor)
- Anti-angiogenic agents (magainin analogs (anti-microbial agent, (Ala(8,13,18))-magainin II amide, inhibits pregnancy establishment during blastocyst implantation) and fumagillin (Fumagilin-B is used for the control of Nosema in honey bees. Nosema impairs the digestive process and causes premature aging and death in worker bees).

And finally a WHO representative concludes: For women to benefit from these new technologies, they need better access to education and income and to have greater decision-making power [1].

References Based on Internet Links:

- Cochrane Collaboration Topic: Fertility Regulation http://www.cochrane.org/reviews/en/topics/64.html
- Science, medicine, and the future: Contraception – Baird et al. http://bmj.bmjjournals.com/cgi/content/full/319/7215/969

References:

1. D'Arcangues C. Future methods of fertility regulation. Training in Reproductive Health Research. World Health Organization, Geneva, 2006. http://www.gfmer.ch/Medical_education_En/PGC_RH_2006/pdf/Future_Methods_Darcangues_2006.pdf

2. Petitti D. Combination estrogen-progestin oral contraceptives. N Engl J Med 2003; 349: 1443–50.

3. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. Cochrane Database Syst Rev 2007; (1): CD004425.

4. Yonkers KA. Antidepressants in the treatment of premenstrual dysphoric disorder. Clin Psychiatry 1997: 589 (Suppl 14): 4–10.

5. Freeman EW, Halbreich U. Premenstrual syndromes. Psychopharmacol Bull 1998: 34: 291–305.

6. Tucker VS, Whalen RE. Premenstrual syndrome. Int J Psychiatry Med 1991; 21: 311–41.

7. Lin J, Thompson DS. Treating premenstrual dysphoric disorder using serotonin agents. J Womens Health Gend Based Med 2001; 10: 745–50.

8. Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database Syst Rev 2006; (1): CD003987.

9. Should body weight influence choice of pill? http://www.contraceptiononline.org/contrarepport/article01-cfm?art=261

10. Ruffing JA, Nieves JW, Zion M, Tendy S, Garrett P, Lindsay R, Cosman F. The influence of lifestyle, menstrual function and oral contraceptive use on bone mass and size in female military cadets. Nutr Metab (Lond) 2007; 4: 17.

11. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, Zikan M, Dusek L. Hormonal contraception and risk of cancer. Hum Reprod Update 2010. doi:10.1093/humupd/dmq022.

12. Singletary SE. Rating the risk factors for breast cancer. Ann Surg 2003; 237: 474–82.

13. Fletcher SW. Risk Factors for Breast Cancer (May 11, 2006). Retrieved July 9, 2006 at: http://patients.uptodate.com/topic.asp?title=breast+cancer+reduction&file=cancer/2174mark=1&submit=find.

14. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996; 347: 1713–27.

15. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, Bernstein L, Malone KE, Ursin G, Strom BL, Norman SA, Wingo PA, Burkman RT, Berlin JA, Simon MS, Spirtas R, Weiss LK. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002; 346: 2025–32.

16. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010; 340: 927.

17. Silvera SA, Miller AB, Rohan TE. Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. Cancer Causes Control 2005; 16: 1059–63.

18. Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andrulis IL, West DW, Li FP, Southey MC, Giles GG, McCredie MRE, Hopper JL, Whittemore AS for the Breast Cancer Family Registry. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005; 14: 350–6.

19. Hankinson SE, Colditz GA, Hunter DJ, Spencer TL, Rosner B, Stampfer MJ. A quantitative assessment of oral contraceptive use and risk of ovarian cancer. Obstet Gynecol 1992; 80: 708–14.

20. The reduction in risk of ovarian cancer associated with oral contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. N Engl J Med 1987; 316: 650–5.

21. Schildkraut JM, Calingaert B, Marchbanks PA, Moorman PG, Rodriguez GC. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. J Natl Cancer Inst 2002; 94: 32–8.

22. Greer JB, Modugno F, Allen GO, Ness RB. Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. Obstet Gynecol 2005; 105: 731–40.

23. Lurie G, Thompson P, McDuffie KE, Carney ME, Terada KY, Goodman MT. Association of estrogen and progestin potency of oral contraceptives with ovarian carcinoma risk. Obstet Gynecol 2007; 109: 597–607.

24. Narod SA, Risch H, Moslehi R, Dørum A, Neuhausen S, Olsson H, Provencher D, Radice P, Evans G, Bishop S, Brunet JS, Ponder BA. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998; 339: 424–8.

25. Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, Ben-Baruch G, Fishman A, Menczer J, Ebbers SM, Tucker MA, Wacholder S, Struewing JP, Friedman E, Piura B; National Israel Ovarian Cancer Study Group. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001; 345: 235–40.

26. Franceschi S. The IARC commitment to cancer prevention: the example of papillomavirus and cervical cancer. Recent Results Cancer Res 2005; 166: 277–97.

27. Smith JS, Bosetti C, Muñoz N, Herrero R, Bosch FX, Eluf-Neto J, Meijer CJ, Van Den Brule AJ, Franceschi S, Peeling RW; IARC multicentric case-control study. Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study. Int J Cancer 2004; 111: 431–9.

28. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de González A, Colin D, Franceschi S, Goodill A, Green J, Peto J, Plummer M, Sweetland S. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006; 118: 1481–95.

29. Smith JS, Green J, Berrington de González A, Appleby P, Peto J, Plummer M, Franceschi S, Beral V. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003; 361: 1159–67.

30. Moreno V, Bosch FX, Muñoz N, Meijer CJ, Shah KV, Walboomers JM, Herrero R, Franceschi S; International Agency for Research on Cancer. Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet 2002; 359: 1085–92.

31. Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 2004; 127 (Suppl 1): 72–8.

32. Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ 2007; 335: 651.

33. Meirik O, Farley TMM. Risk of cancer and the oral contraceptive pill. BMJ 2007; 335: 621–2.

34. Gallo MF, Grimes DA, Schulz KF, d'Arcangues C, Lopez LM. Combination injectable contraceptives for contraception. Cochrane Database Syst Rev 2005; (3): CD004568.

35. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. Eur J Contracept Reprod Health Care 1998; 3: 169–78.

36. van Vliet HA, Grimes DA, Lopez LM, Schulz KF, Helmerhorst FM. Triphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2006; (3): CD003553.

37. van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus triphasic oral contraceptives for contraception. Cochrane Database Syst Rev 2006; (3): CD003283.

38. Archer DF, Jensen JT, Johnson JV, Borisute H, Grubb GS, Constantine GD. Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. Contraception 2006; 74: 439–45.

39. Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. Cochrane Database Syst Rev 2005; (3): CD004695.

40. Bundeszentrale für gesundheitliche Aufklärung (BZgA). Verhütungsverhalten Erwachsener. Ergebnisse der Repräsentativbefragung 2007.

41. Astedt B, Jeppsson S, Liedholm P, Rannevik G, Svanberg L. Clinical trial of a new oral contraceptive pill containing the natural oestrogen 17 beta-oestradiol. Br J Obstet Gynaecol 1979; 86: 732–6.

42. Csemiczky G, Dieben T, Coeling Bennink HJ, Landgren BM. The pharmacodynamic effects of an oral contraceptive containing 3 mg micronized 17 beta-estradiol and 0.150 mg desogestrel for 21 days, followed by 0.030 mg desogestrel only for 7 days. Contraception 1996; 54: 333–8.

43. Hirvonen E, Allonen H, Anttila M, et al. Oral contraceptive containing natural estradiol for premenopausal women. Maturitas 1995; 21: 27–32.

44. Timmer CJ, Geurts TB. Bioequivalence assessment of three different estradiol formulations in postmenopausal women in an open, randomised, single-dose, 3-way cross-over study. Eur J Drug Metab Pharmacokinet 1999; 24: 47–53.

45. Oettel M, Breitbarth H, Elger W, et al. The pharmacological profile of dienogest. Eur J Contracept Reprod Health Care 1999; 4 (Suppl 1): 2–13.

46. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 2000; 62: 29–38.

47. Zeun S, Lu M, Uddin A, Zeiler B, Morrison D, Blode H. Pharmacokinetics of an oral contraceptive containing oestradiol valerate and dienogest. Eur J Contracept Reprod Health Care 2009; 14: 221–32.

48. Ahrendt HJ, Makalova D, Parke S, et al. Bleeding pattern and cycle control with an estradiol-based oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. Contraception 2009; 80: 436–44.

49. Fraser IS, Zeun S, Machlitt A, Mellinger U. A novel oral contraceptive comprising estradiol valerate/dienogest for the treatment of heavy and/or prolonged menstrual bleeding without organic cause: a double-blind, randomised, placebo-controlled trial. Int J Gynecol Obstet 2009; 107 (Suppl 2): S183

50. Jensen J, Machlitt A, Mellinger U, Schaefers M, Fraser IS. A multicenter, double-blind, randomized, placebo-controlled study of oral estradiol valerate/dienogest for the treatment of heavy and/or prolonged menstrual bleeding. Fertil Steril 2009; 92: S32.

51. Richards JS, Russell DL, Ochsner S, Espey LL. Ovulation: new dimensions and new regulators of the linflammatory-like response. Annu Rev Physiol 2002; 64: 69–92.

52. Matousek M, Mitsube K, Mikuni M, Brännström M. Inhibition of ovulation in the rat by a leukotriene B4 receptor antagonist. Mol Hum Reprod 2001; 7: 35–42.

53. Peters MW, Pursley JR, Smith GW. Inhibition of intrafollicular PGE2 synthesis and ovulation following ultrasound-mediated intrafollicular injection of the selective cyclooxygenase-2 inhibitor NS-398 in cattle. J Anim Sci 2004; 82: 1656–62.

54. Gallo MF, Grimes DA, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev 2003; (1): CD003552.

55. Sarkar NN. The combined contraceptive vaginal device (NuvaRing®): A comprehensive review. Euro J Contraception Reprod Health Care 2005; 10: 73–8.

56. Cheng L, Gülmezoglu AM, Van Oel CJ, Piaggio G, Ezcurra E, Van Look PFA. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2004, (3): CD001324. DOI: 10.1002/14651858.CD001324.pub2 http://www.cochrane.org/reviews/en/ab001324.html

57. Gemzell-Danielsson K, Meng CX. Emergency contraception: potential role of ulipristal acetate. Int J Women's Health 2010; 2: 53–61.

58. Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspart A, Ulmann A, Gainer E. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and metaanalysis. Lancet 2010; 13: 555–62.

59. Kulier R, Helmerhorst FM, O'Brien P, Usher-Patel M, d'Arcangues C. Copper containing, framed intra-uterine devices for contraception. Cochrane Database Syst Rev 2006; (3): CD005347.

60. National Institute of Clinical Excellence. Heavy menstrual bleeding. Clinical Guideline 44. ISBN 9781904752356. http://www.rcog.org.uk.

61. Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding. A systematic review and meta-analysis. Obstet Gynecol 2009; 113: 1104–16.

62. Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivelä A, Kujansuu E, Vuorma S, Yliskoski M, Paavonen J. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial five-year followup. JAMA 2004; 291: 1456–63.

63. O'Brien PA, Marfleet C. Frameless versus classical intrauterine device for contraception. Cochrane Database Syst Rev 2005; (1): CD003282.

64. Cook L, Nanda K, Grimes D. Diaphragm versus diaphragm with spermicides for contraception. Cochrane Database Syst Rev 2003; (1): CD002031.

65. Gallo MF, Grimes DA, Schulz KF. Cervical cap versus diaphragm for contraception. Cochrane Database Syst Rev 2002; (4): CD003551.

66. Croxatto HB, Mäkäräinen L. The pharmacodynamics and efficacy of Implanon®. An overview of the data. Contraception 1998; 58: 91S–97S.

67. Mäkäräinen L, van Beek A, et al. Ovarian function during the use of a single contraceptive implant: Implanon® compared with Norplant®. Fertil Steril 1998; 69: 714–21.

68. Huber J. Pharmacokinetics of Implanon®: An integrated analysis. Contraception 1998; 58: 85S–90S.

69. Geurts TBP, Goorissen EM, et al. Summary of drug interactions with oral contraceptives. Summ Drug Interact Oral Contracept 1993: 11–93.

70. Graesslin O, Korver T. The contraceptive efficacy of Implanon®: A review of clinical trials and marketing experience. Eur J Contracept Reproduct Health Care 2008; 13: 4–12.

71. Blumenthal PD, Gemzell-Danielsson K, et al. Tolerability and clinical safety of Implanon®. Eur J Contracept Reprod Health Care 2008; 13: 29–36.

72. Darney P, Patel A, et al. Safety and efficacy of a single-rod etonogestrel implant (Implanon®): results from 11 international clinical trials. Fertil Steril 2009; 91: 1646–53.

73. Mansour D, Korver T, et al. The effects of Implanon® on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008; 13: 13–28.

74. Urbancsek J. An integrated analysis of non-menstrual adverse events with Implanon®. Contraception 1998; 58: 109S–115S.

75. Beerthuizen R, Van Beek A, et al. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon® compared to a nonhormonal method of contraception. Human Reprod 2000; 15: 118–22.

76. Bahamondes L, MonteiroDantas C, et al. A prospective study of the forearm bone density of users of etonorgestrel and levonorgestrel-releasing contraceptive implants. Hum Reprod 2006; 21: 466–70.

77. Reinprayoon D, Taneepanichskul S, et al. Effects of the etonogestrel-releasing contraceptive implant (Implanon®) on parameters of breastfeeding compared to those of an intrauterine device. Contraception 2000; 62: 239–46.

78. Taneepanichskul S, Reinprayoon D, et al. Effects of the etonogestrel-releasing implant Implanon® and a nonmedicated intrauterine device on the growth of breast-fed infants. Contraception 2006; 73: 368–71.

79. WHO. Medical eligibility criteria for contraceptive use. 4. Edition, 2009.

80. Lantz A, Nosher JL, et al. Ultrasound characteristics of subdermally implanted Implanon® contraceptive rods. Contraception 1997; 56: 323–7.

81. Merki-Feld GS, Brekenfeld C, et al. Nonpalpable ultrasonographically not detectable Implanon® rods can be localized by magnetic resonance imaging. Contraception 2001; 63: 325–8.

82. Prosch W, Walter RM, et al. Sonografische Lokalisation nicht tastbarer Implanon® Hormonimplantate. Ultraschall in Med 2008; 29: 239–44.

83. Funk S, Miller MM et al. Safety and efficacy of Implanon, a single-rod implantable contraceptive containing etonogestrel. Contraception 2005; 71: 319–26.

84. Arzneimittelkommission der deutschen Ärzteschaft. „Aus der UAWDatenbank": Misslungene Explantation des implantierbaren Kontrazeptivums Implanon®. Dt Ärzteblatt 2006; 103: A-1771, B-1519, C-1471.

85. Jacobstein R. Long-acting and permanent contraception: an international development, service delivery perspective. J Midwifery Womens Health 2007; 52: 361–7.

86. Power J, French R, Cowan F. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Cochrane Database Syst Rev 2007; (3): CD001326.

87. Department of Reproductive Health and Research, World Health Organization. WHO statement on hormonal contraception and bone health. Contraception 2006; 73: 443–44.

88. Draper BH, Morroni C, Hoffman M, Smit J, Beksinska M, Hapgood J, Van der Merwe L. Depot medroxyprogesterone versus norethisterone oenanthate for long-acting progestogenic contraception. Cochrane Database Syst Rev 2006; (3): CD005214.

89. Jain J, et al. Contraceptive efficacy and safety of DMPA-SC. Contraception 2004; 70: 269–75.

90. Jain J, et al. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of DepoProvera®. Contraception 2004; 70: 11–8.

91. Curtis KM, Martins SL. Progestin-only contraception and bone mineral density: a systematic review. Contraception 2006; 73: 470–87.

92. Orr-Walker BJ, Evans MC, Ames RW, Clearwater JM, Cundy T, Reid IR. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal postmenopausal women. Clinical Endocrinology 1998; 49: 515–8.

93. Grimes DA, Gallo MF, Halpern V, Nanda K, Schulz KF. Fertility awareness-based methods for contraception. Cochrane Database Syst Rev 2004; (4): CD004860.

94. Frank-Herrmann P, Heil J, Gnoth C, Toledo E, Baur S, Pyper C et al. The effectiveness of a fertility awareness based method to avoid pregnancy in relation to a couple's sexual behaviour during the fertile time: a prospective longitudinal study. Hum Reprod 2007; 22: 1310–19.

95. The European NFP study groups. European multicenter study of natural family planning (1989–95): efficacy and dropout. Adv Contracept 1999; 15: 69–83.

96. Freundl G, Godehardt E, Kern P, Frank-Herrmann P, Koubenec H, Gnoth C. Estimated maximum failure rates of cycle monitors using daily conception probabilities in the menstrual cycle. Hum Reprod 2003; 18: 2628–33.

97. Scott A, Glasier A. Contraceptive sterilization: global issues and trends. Bull World Health Organ 2003; 81: 146.

98. Nardin JM, Kulier R, Boulvain M, Peterson HB. Techniques for the interruption of tubal patency for female sterilisation. Cochrane Database Syst Rev 2002; (4): CD003034.

99. Kulier R, Boulvain M, Walker D, De Candolle G, Campana A. Minilaparotomy and endoscopic techniques for tubal sterilisation. Cochrane Database of Systematic Reviews 2004, (3): CD001328. DOI: 10.1002/14651858.CD001328.pub2 http://www.cochrane.org/reviews/en/ab001328.html

100. Naz RK. Vaccine for contraception targeting sperm. Immunol Rev 1999; 171: 193–202.

101. Baird DT. Overview of advances in contraception. Br Med Bull 2000; 56: 704–16.

Further References:

– Archer DF, Jensen JT, Johnson JV, Borisute H, Grubb GS, Constantine GD. Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. Contraception 2006; 74 (6): 439–45.

– Bayer-Schering-Pharma 2007. Personal information.

– Centers for Disease Control and Prevention and the National Institute of Child Health and Human Development. The reduction in risk of ovarian cancer associated with oral-contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. NEJM 1987; 316: 650–5.

– Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996; 347: 1713–27.

– Collaborative Study Group on the Desogestrel containing Progestogen only Pill. A double blind study comparing the contraceptive efficacy, acceptability and safety of two

progestogen only pills containing desogestrel 75 µg/day or levonorgestrel 30 µg/day. Euro J Contraception Reprod Health Care 1998; 3: 169–78.

– Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle versus cyclic use of combined oral contraceptives for contraception. Cochrane Database of Systematic Reviews 2005, (3): CD004695. DOI: 10.1002/14651858.CD004695.pub2 http://www.cochrane.org/reviews/en/ab004695.html
– Franceschi S. The IARC commitment to cancer prevention: The example of papillomavirus and cervical cancer. Recent Results in Cancer Research 2005; 166: 277–97.
– Gallo MF, Grimes DA, Schulz KF, d'Arcangues C, Lopez LM. Combination injectable contraceptives for contraception. Cochrane Database of Systematic Reviews 2005, (3): CD004568. DOI: 10.1002/14651858.CD004568.pub2 http://www.cochrane.org/reviews/en/ab004568.html
– Greer JB, Modugno F, Allen GO, Ness RB. Androgenic progestins in oral contraceptives and the risk of epithelial ovarian cancer. Obstetrics and Gynecology 2005; 105: 731–740.
– Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ 2007; 335: 651.
– Hankinson SE, Colditz GA, Hunter DJ, Spencer TL, Rosner B, Stampfer MJ. A quantitative assessment of oral contraceptive use and risk of ovarian cancer. Obstet Gynecol 1992; 80: 708–14.
– IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 72: Hormonal Contraception and Postmenopausal Hormonal Therapy. WHO/IARC, Lyon, 1999.
– International collaboration of epidemiological studies of cervical cancer: carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006; 118: 1481–95.
– Kulier R, Helmerhorst FM, O'Brien P, Usher-Patel M, d'Arcangues C. Copper containing, framed intrauterine devices for contraception. Cochrane Database of Systematic Reviews 2006, (3): CD005347. DOI: 10.1002/14651858.CD005347.pub2. http://www.cochrane.org/reviews/en/ab005347.html
– Lurie G, Thompson P, McDuffie KE, Carney ME, Terada KY, Goodman MT. Association of estrogen and progestin potency of oral contraceptives with ovarian carcinoma risk. Obstet Gynecol 2007; 109: 597–607.
– Marchbanks PA, McDonald CA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. NEJM 2002; 346: 2325–32.
– Meirik O, Farley TMM. Risk of cancer and the oral contraceptive pill. Editorial. BMJ, doi:10.1136/bmj.39336.503067.BE.
– Mime RL, Knight JA. John EM, et al. Oral contraceptive use and risk of earlyonset breast cancer in carriers and noncarriers of BRCAI and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005; 14: 350–5.
– Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. NEJM 2001; 345: 235–40.
– Moreno V, Bosch FX, Munoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: The IARC multicentric case-control study. Lancet 2002; 359: 1085–92.
– Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. NEJM 1998; 339: 424–8.
– Organon 2007. Personal information.
– Schildkraut JM, Calingaert B, Marchbanks PA, Moorman PG, Rodriguez GC. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. J Nat Cancer Inst 2002; 94: 32–8.
– Silvera SA, Miller AB, Rohan TE. Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. Cancer Causes Control 2005; 16: 1059–63.
– Singletary SE. Rating the risk factors for breast cancer. Ann Surg 2003: 237: 474–82.
– Smith JS, Green J, Berrington de GA, et al. Cervical cancer and use of hormonal contraceptives: A systematic review. Lancet 2003; 361: 1159–67.
– Smith JS, Bosetti C, Munoz N, et al. IARC multicentric case control study: Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric casecontrol study. Int J Cancer 2004; 111: 431–39.
– van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF, Lopez LM. Bphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2006; (3): CD002032. DOI 10.1002/14651858.CD002032.pub2.
– Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. Gastroenterology 2004; 127 (5 Suppl 1): 72–8.

Further Internet Links:

– Fletcher SW. Patient information: Risk factors for breast cancer 2008. www.uptodate.com/patients
– Holden Comprehensive Cancer Center, Cancer Information Service. Ovarian Cancer Protective Factors and Risk Factors; last revised 5/2003
– Online: www.uihealthcare.com/topics/medicaldepartments/cancercenter/cancertips/ovarianfactors.html
– FDA Updates Labeling for Ortho Evra Contraceptive Patch (2005). www.fda.gov/bbs/topics/news/2005/NEW01262.htm

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