

Journal für

Reproduktionsmedizin und Endokrinologie

– Journal of Reproductive Medicine and Endocrinology –

Andrologie • Embryologie & Biologie • Endokrinologie • Ethik & Recht • Genetik
Gynäkologie • Kontrazeption • Psychosomatik • Reproduktionsmedizin • Urologie



Contraception - Update and Trends

Rabe T

J. Reproduktionsmed. Endokrinol 2007; 4 (6), 337-357

www.kup.at/repromedizin

Online-Datenbank mit Autoren- und Stichwortsuche

Offizielles Organ: AGRBM, BRZ, DVR, DGA, DGGEF, DGRM, D-I-R, EFA, OEGRM, SRBM/DGE

Indexed in EMBASE/Excerpta Medica/Scopus

Krause & Pachernegg GmbH, Verlag für Medizin und Wirtschaft, A-3003 Gablitz



ENDO FERTI FORUM

ENDOKRINOLOGIE & FERTILITÄT
FÜR KLINIK & PRAXIS

20.-21. März 2026

Universitätsmedizin Mainz

Einladung zu unserer wissenschaftlichen Veranstaltung Endo-Ferti-Forum

Brücke(n) zwischen Unikliniken und Praxen an Rhein und Main(z)

– die aus dem bisherigen Format „Ferti Forum“ ab 2026 hervorgeht –



Freuen Sie sich auf spannende Vorträge und den lebendigen Austausch mit Kolleg:innen und Expert:innen aus Klinik und Praxis. Freitagabend laden wir Sie herzlich zu einem entspannten Empfang ein – eine perfekte Gelegenheit, Kontakte zu knüpfen und den Tag genussvoll ausklingen zu lassen.

Wissenschaftliche Leitung: Univ.-Professorin Annette Hasenburg, Dr. Susanne Theis, Universitätsmedizin Mainz, Sanitätsrat Dr. Werner Harlfinger, BVF Rheinland-Pfalz Dr. Rüdiger Gaase, BVF Hessen Dr. Klaus J. Doubek

Schirmherrschaften: Prof. Nicole Sänger, Uniklinik Bonn, Prof. Jan-Steffen Krüssel, Uniklinik Düsseldorf, Dr. Annette Bachmann, Uniklinik Frankfurt am Main, Prof. Christine Skala, Uniklinik Köln

Weitere Informationen
& Anmeldung unter



Contraception – Update and Trends

T. Rabe

In the future, fertility control 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) and on new targets for contraception. Counselling of women in view of contraceptive choices based on individual risks (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, Wyeth-Ayerst, Ortho-McNeil and Organon.

Female contraception: Ovulation inhibition: In the future, a focus will be placed on the preselection of patients to minimize their individual risk, new oral contraceptive (OC) regimen, OC with new progestins, OC with estradiol or estradiolesters, new ovulation inhibitors with new progestins and new regimens including long cycles and continuous steroidal contraceptives, new contraceptive patches, vaginal rings, spray-on contraceptives, recently identified genes involved in the ovulation process as new targets for ovulation inhibitors.

Fertilisation inhibition: New intrauterine systems will comprise: a smaller Mirena intrauterine system releasing levonorgestrel (LNG) and new frameless progestin-releasing intrauterine systems (IUS). Various new contraceptive barriers have been introduced. Research is ongoing on substances acting both as spermicides and as microbicides, reducing the risk of sexually transmitted diseases. New implantables and injectables will feature an improved pharmacokinetic profile, decreased side effects and a safer delivery system. Additionally, there are various new approaches in female sterilisation. Immunocontraception for the female will not be available in the near future.

Implantation inhibition: Selective progesterone receptor modulators (SPRMs) are tested for postcoital contraception. New targets are analysed for immunocontraceptives.

Male contraception: Condoms and vasectomy are the “gold standards” in male contraception. The development of hormonal contraceptives for men has recently been stopped by Bayer-Schering-Pharma and Organon.

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* 2007; 4 (6): 337–57.

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

Both, the United Nations (UN) and the World Bank predict that until the year 2025 80–90 % of the global population growth will occur in so-called developing countries: 50 % will be accounted for by an increasing life expectancy due to improved medical care, 17 % by couples having more than two children, and 33 % by children born after unwanted pregnancies.

Within the next two to three decades, the demand for fertility control is expected to increase as the number of couples in the reproductive age group 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

- UNFPA, the United Nations Population Fund
<http://www.unfpa.org/>
- Population Issues in the 21st Century, The Role of the World Bank
<http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/281627-1095698140167/PopulationDiscussionPaperApril07Final.pdf>
- World Bank: Population and Development
<http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTHEALTHNUTRITIONANDPOPULATION/EXTPRH/0,,contentMDK:20341152~menuPK:650489~pagePK:148956~piPK:216618~theSitePK:376855,00.html>

- World Bank: Population and the World Bank: PDF download via:
<http://wbIn0018.worldbank.org/HDNet/HDdocs.nsf/c0d65c5ea6fcb4688525670c004d14c2/1c1ff45b5648682c8525680f006c2d2c?OpenDocument>
- World Bank: Population and Reproductive Health
<http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTHEALTHNUTRITIONANDPOPULATION/EXTPRH/0,,menuPK:376861~pagePK:149018~piPK:149093~theSitePK:376855,00.html>
- The world's growing population [PDF]
[http://wbIn0018.worldbank.org/HDNet/hddocs.nsf/65538a343139acab85256cb70055e6ed/8ebf48e0f2ac79c385256e00005eb785/\\$FILE/Growing%20Population.pdf](http://wbIn0018.worldbank.org/HDNet/hddocs.nsf/65538a343139acab85256cb70055e6ed/8ebf48e0f2ac79c385256e00005eb785/$FILE/Growing%20Population.pdf)
- WHO, Geneva, Switzerland
<http://www.who.int/reproductive-health/>
- The World at Six Billion United Nations – Introduction [PDF]
<http://www.un.org/esa/population/publications/sixbillion/sixbilbiblio.pdf>
- World population – Wikipedia, the free encyclopedia. Current projections by the UN 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

Received: September 12, 2007; accepted after revision: November 26, 2007.

From the Department of Gynecological Endocrinology and Reproductive Medicine, Medical School Heidelberg Germany

Correspondence: Thomas Rabe, MD, PhD, MD (hons), Professor Obstetrics and Gynecology, Department of Gynecological Endocrinology and Reproductive Medicine, University Women's Hospital, Medical School Heidelberg, D-69115 Heidelberg, Voßstraße 9; e-mail: thomas_rabe@yahoo.de

1. 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, and their acceptability is limited by side effects and inconvenience. Even in developed countries where contraception is freely available, many

unplanned pregnancies occur. Thus, there is 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 contraceptives but also the development of new methods. The age of onset of sexual activity decreases, while childbearing is being delayed or, in many developed countries, altogether forgone. 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 be of 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 they are offered, or are deterred from using contraceptives due to the side effects of available methods. The crucial issues in the future will therefore be aimed at optimizing the use of currently available methods and at making them safe, effective, and acceptable, with minor alterations in composition or delivery system. In addition, there should be new developments in contraceptive technology.

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

2. 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),
- reversibility (f/m),
- no negative effect on libido (f/m),
- easy to use (f/m),
- not expensive (f/m),
- worldwide availability (f/m),
- worldwide acceptance based on religious, political, and ethical considerations (f/m),
- offering “non-contraceptive benefits” (f/m) – features that arouse 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 menstrual bleedings (f), improvement of dysmenorrhoea (f), improvement of premenstrual syndrome (f).

3. Research in the Field of Contraception

Research on new contraceptives is only done by Bayer-Schering-Pharma, Wyeth-Ayerst, Ortho-MacNeil and Organon; 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, with costs amounting to 400–800 million US\$.

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: mode of action
3. New targets for contraception.

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

• Internet Links

- 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
- WHO Research on Reproductive Health. Biennial Report 2004–2005: Sexual and reproductive health – laying the foundation for a more just world through research and action
http://www.who.int/reproductive-health/publications/biennial_reports/2004_05/report.pdf

4. Female Contraception

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

For some contraceptive methods, Cochrane analyses are available. But these analyses can only be as good as the underlying studies. Because of the importance of placebo-controlled randomized trials these studies must be carefully analysed in view of e. g. sample size, origin, selection, performance of the study, drop-outs and other bias, which may lead to wrong conclusions (e. g. Women's Health Initiative Study).

4.1 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 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), estrogen-free 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 provided by Bayer-Schering-Pharma, 2007, and Organon, 2007).

4.1.1 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, dienogest) derivatives of 17-hydroxyprogesterone.

ne (e. g. chlormadinone acetate, cyproterone acetate) or spiro lactone derivatives (drospirenone) and 15–35 µg ethinyl-estradiol per tablet.

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 anti-androgens (cyproterone acetate, chlormadinone acetate, dienogest, and drospirenone) are preferred by more than 60 % of all women in the reproductive age (personal information provided by Bayer-Schering-Pharma, 2007), but mild acne can also be improved by using various oral contraceptives. In their Cochrane analysis, Arowojolu et al [3] 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 in reducing facial acne. When comparing pills with different hormones, no important differences were found.

OC and brain:

OC may lead to mood changes.

Depressive mood and/or 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 disorder (PMDD), is 2–9 % [4–7].

Depressive mood occurring in patients with premenstrual syndrome may improve through use of oral contraceptives; an extended cycle may be of some advantage, too.

- A 24-day regimen with drospirenone called “YAZ” has recently been approved in the US for the treatment of emotional and physical symptoms of premenstrual dysphoric disorder (PMDD), which is a severe form of premenstrual symptoms.
- Depressive mood in OC users might be due to a deficiency of vitamin B₆.

Cardiovascular risk factors:

Family history in view of cardiovascular disease is gaining more and more importance, in view of identifying 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 is important in view of cardiovascular events.

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

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. long-distance travel).

OC and body weight:

Body weight is a very important factor for female self-esteem and well-being.

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

The impact of OCs on body weight does not depend on anabolic effects; steroid hormones can enhance appetite; ethinylestradiol may lead to water retention in the 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.

In a Cochrane analysis, Gallo et al [8] found that contraceptive pills and patches do not lead to major weight gain. Three 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 in the study populations, see also [9].

OC, Bone density and fractures [10]:

A higher bone mineral density (BMD) and a larger bone size attained in childhood, maintained through the third decade of life, have 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 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.

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 since 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 to 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 West Point Military Academy 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. This question must also be clarified for OCs on the market and for new products.

Breast cancer:

Breast cancer incidence rates vary > 10fold worldwide and have increased in most countries in the past few decades. Differences in the prevalence of hormonal and lifestyle factors are likely to explain some of the international variation in incidence. In developed countries more than one of ten women will suffer from breast cancer during their lives.

Risk factors for women in the reproductive age are analysed in various reviews (e. g. [11]):

- Strong risk factors are increasing age, family history and previous breast cancer.
- Moderate risk factors are density of the breasts on mammogram, biopsy abnormalities and exposure to radiation.
- Other risk factors: age at time of reproductive events, no pregnancies and no breastfeeding, height and weight, alcohol consumption, presence of other cancers and miscellaneous factors
- Decreasing the risk are removal of the ovaries, lifestyle changes, medication, early detection, having more than one child, breastfeeding.

A reanalysis of worldwide epidemiologic data on the possible relationship between OCs and the diagnosis of breast cancer was conducted in 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 [12] and the results are as follows:

- Current or recent OC users: 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: ten 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: breast cancer diagnosed in women after 10 or more years of not using OCs was less advanced than breast cancer 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 OCs 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 esti-

mated excess number of cancers diagnosed up to 10 years after stopping use rises from 0.5 to 4.7.

In a big case-control study, Marchbanks et al [13] interviewed a total of 4575 women with breast cancer and 4682 controls who were 35 to 64 years old. The relative risk was 1.0 (0.8–1.3) for women 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 oral contraceptive use at a young age. In conclusion, among women from 35 to 64 years of age, current or former oral contraceptive use was not associated with a significantly increased risk of breast cancer.

Even in patients with a high family history risk for breast cancer and in carriers of BRCA1 mutation, OC seem to have no negative influence on the breast cancer incidence in those subjects [14, 15]. Regular cancer screening including self examination of the breasts is strongly recommended.

Comments:

- The overwhelming evidence in literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses [16–18].
- The Cancer and Steroid Hormone (CASH) study [17] also showed no latent effect on the risk of breast cancer for at least a decade following longterm use.
- A few studies have shown a slightly increased relative risk of developing breast cancer [18–21] although the methodology of these studies, which included differences in examination of users and nonusers and differences in age at start of use, has been questioned [21–23].
- Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use [24, 25]. But nevertheless the incidence of breast cancer in young women is pretty low (1/15000 for the age group < 25 years) (Cancer Research UK, 2004: Breast Cancer Factsheet: (http://www.cancerresearchuk.org/aboutcancer/statistics/statsmisc/pdfs/factsheet_breast_feb2004.pdf) and these data with older higher dose pills should not be overestimated in clinical practice, when counselling adolescents.
- Overall, oral contraceptive use had neither a harmful nor a beneficial effect on breast cancer mortality. The differences between pill users and nonusers were slight, and the risk estimates were usually reduced with confidence limits that nearly always included [26].
- The question of why there is a higher detection rate of breast cancer in OC users (earlier detection of pre-existing tumours) or a higher lifetime risk (additional new tumours in OC users) has not been settled so far.
- 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); this cannot explain the higher detection rate of breast cancers in young women.

- In postmenopausal women, the lower incidence of HRT use has recently led to a lower rate of breast cancer cases diagnosed, but finally it cannot be excluded that women without HRT not as much motivated for breast cancer screening than those on HRT.

Ovarian cancer:

- Epidemiology: <http://www.tumorzentrum-son.de/leitlinien/documents/Leitlinien%20Ovarialkarzinom%20TUZSON%2002-2006.pdf>: ovarian cancer is the second-most frequent genital tumour of women in Germany.

Incidence: new cases amount to 15/100,000 women with a peak at 50–60 years; at the age of 45: 40/100,000; at the age of 70: 50/100,000. In 2/3 of all cases, first diagnosis happens at Figo stages III and IV.

- Risk factors: patients with genetic predisposition (BRCA-1 and 2) find themselves in a high-risk situation and account for approximately 10 % of all cases.

According to the Holden Comprehensive Cancer Center, Cancer Information Service (2007): the risk factors known to increase the chance of developing ovarian cancer are family history, hormone replacement therapy, talcum powder, fertility drugs and a high-fat diet. Protective factors for ovarian cancer are: oral contraceptives, child-bearing and breast-feeding, tubal ligation and hysterectomy.

• Internet Links

Holden Comprehensive Cancer Center, Cancer Information Service (2007): Ovarian Cancer Protective Factors and Risk Factors; last update 5/2003

Online: <http://www.uihealthcare.com/topics/medicaldepartments/cancercenter/cancertips/ovarianfactors.html>

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

Duration of use: OCs reduce the risk of ovarian cancer. In an analysis of 20 studies of OC use and ovarian cancer, researchers from the Harvard Medical School found that the risk of ovarian cancer decreased with increasing duration of OC use. Results showed a 10–12 % decrease in risk after 1 year of use, and an approximate 50 % decrease after 5 years of use [27].

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 [28]. 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 [29]. In another recent study, the Steroid Hormones and Reproductions (SHARE) study, researchers investigated new, lower-dose progestins with varying androgenic properties (testosterone-like effects). They found no difference in ovarian cancer risk between androgenic and non-androgenic pills [30].

IACR analysis (1999) (<http://www.inchem.org/documents/iarc/vol72/vol72-1.html>): four cohort and 21 case control

studies addressed the relationship between ovarian cancer and use of combined OCs.

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 recently 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 [31].

Genetic risk factors: OC use by 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 [32, 33].

Endometrial cancer:

A meta-analysis by the IACR (1999) included three cohort and 16 case control 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 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 (<http://www.cancer.gov/cancertopics/factsheet/Risk/oral-contraceptives>):

Increased risk: evidence shows that long-term use of OCs (5 or more years) may be associated with an increased risk of cancer of the cervix [34].

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 [34]. More information about HPV and cancer is available at <http://www.cancer.gov/cancertopics/factsheet/risk/HPV>.

Further risk factors are chlamydia infection [35] and cigarette smoking [36].

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 [37].
- In another IARC report, data from eight studies were combined to assess the effect of OC use on cervical cancer risk in HPV-positive women. Researchers found a fourfold increase in risk among women who had used OCs for more 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 [38].
- The IARC is planning a study to reanalyze all data related to OC use and cervical cancer risk [34].

Regular cancer screening including cervix cytology is strongly recommended.

Liver cancer:

Summary according to a recent statement of the National Cancer Institute (US) (<http://www.cancer.gov/cancertopics/factsheet/Risk/oral-contraceptives>):

- Several studies have found that OCs increase the risk of liver cancer in populations usually considered at low risk, such as white women in the US and Europe who do not have any liver disease. In these studies, women who used OCs for longer periods of time were found to be at an increased risk for liver cancer.
- However, OCs did not increase the risk of liver cancer in Asian and African women, who are considered at high risk for this disease. Researchers believe this is because other risk factors, such as hepatitis infection, outweigh the effect of OCs [39].

Various cancer risks:

A recent online publication by Hannaford [40] deals with the overall cancer risk of OCs. 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 [41] points out 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 ethinylestradiol (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 ethinylestradiol dosage per tablet from 30–35 to 0 µg per tablet led only to a further reduction of DVT.
- Low-dose pills (20 µg vs > 20 µg ethinylestradiol/tablet) [42]: in this Cochrane analysis, the studies found that more women taking pills with less estrogen quit early and that they had more disruptions to bleeding patterns than women using pills with more estrogen. This review was not able to detect differences in the ability of low-estrogen pills to prevent pregnancies.
- Estrogen-free contraceptives (Cerazette, Organon) (desogestrel-only pill): apart from inducing a local bar-

rier, 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 pills. Pearl Indices of the desogestrel POP and of COC have not been compared directly. At the onset of 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 [43].

Regimen of oral contraceptives:

- Biphasic vs monophasic OCs: in a Cochrane analysis, van Vliet et al [44] did not find enough evidence to say if two-phase pills are more efficient than one-phase types for birth control, bleeding patterns or staying on the pill. 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 analysis due to lack of data.*)
- Biphasic vs triphasic oral contraceptives: in a Cochrane analysis, van Vliet et al [44] showed that available trials did not provide enough evidence to say if three-phase pills worked any better than two-phase types for birth control, bleeding patterns or staying on the pill. More research is needed to show whether three-phase pills are better than two-phase pills. However, two-phase pills are not used frequently enough to warrant further research. (*Author's comment: weak Cochrane analysis due to lack of data.*)
- Continuous daily regimen for 3 months: in the US, two 3-month pills are available: Seasonale (84 days 30 µg ethinylestradiol/150 µg levonorgestrel/7 days hormone-free) and Seasonique (84 days 30 µg ethinylestradiol/150 µg levonorgestrel/7 days 10 µg ethinylestradiol).
- Continuous daily regimen: in 2007, the US Food and Drug Administration (FDA) approved Lybrel (90 µg levonorgestrel/20 µg ethinylestradiol tablets) (Wyeth-Ayerst) for a low-dose, continuous, non-cyclic combination oral contraceptive. In clinical trials (n = 2134) performed by the Conrad Program (US) (2006), a Pearl Index of 1.26 and absence of bleeding in 79 % were reported [45].
- 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).

In a Cochrane analysis of Edelman et al [46], oral contraceptives taken continuously for more than 28 days compare favourably to traditional cyclic oral contraceptives. Six randomized controlled trials met the inclusion criteria. Study findings were similar between 28-day and extended cycles with 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.



Figure 1: Spray-on contraceptive. Reprint with Permission from "Museum für Verhütung und Schwangerschaftsabbruch", Wien, www.muvs.org.

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

• Trends

In the near future, new regimens with estradiol valerate in combination with dienogest (Bayer-Schering-Pharma) and with natural estrogens (estradiol) in combination with norgestrel acetate (Organon) will be available.

24-day regimen: recently the FDA approved a 24-day regimen pill with drospirenone (YAZ) (Bayer-Schering-Pharma) which will be available in Europe 2008. At the same time another 24-day pill with chlormadinone acetate and 20 µg ethinylestradiol will be available (brand name: Belara low)(Grünenthal GmbH).

Other targets for oral contraceptives include the development of estrogen-free contraceptives. Clinical trials are ongoing for spray-on 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 being tested for contraception (e. g., norgestrel acetate, norgestrel, trimegestone) which can be used for oral contraception, vaginal rings, transdermal contraception via patches or gel and for hormone replacement therapy (HRT).

Research: research focuses on recent endocrine, biochemical and genetic information that has been derived

mainly 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 ovary must undergo a series of closely regulated events; each of them may be a target of new substances suitable for ovulation inhibition. Small follicles must mature to the pre-ovulatory 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 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 pre-ovulatory 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 [47].

There is special interest in leukotriene inhibitors, new inhibitors of inflammatory-like response and prostaglandins [47]. 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; meiosis inhibitor factor and inhibitors of meiosis-activating compounds, MPF (maturation-promoting factor), OMI (oocyte maturation inhibitor) [48, 49]. Research is ongoing for new OC formulations with addition of cardioprotective agents. To minimize the cardiovascular risk, especially for perimenopausal women, new guidelines are necessary to improve contraceptive safety.

• Internet Links

- Guidelines for prescribing combined oral contraceptives.
<http://bmj.bmjournals.com/cgi/content/full/312/7023/121/a>
- 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>

4.1.2 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

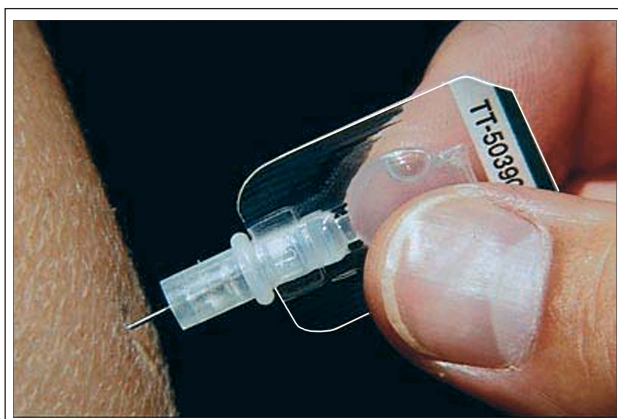


Figure 2: Uniject: the subcutaneous DMPA formulation will be available as a single-use syringe. Reproduced with permission. Copyright Program for Appropriate Technology in Health (PATH). All rights reserved.

days) were approved by the FDA in 2000 but production was stopped due to problems in manufacturing.

In their Cochrane analysis, Gallo et al [42] analysed combination injectable contraceptives and found that combination injectable contraception results in fewer bleeding disruptions and fewer women stopping use for bleeding reasons than progestin-only 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 progestin-only 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 self-injectable (Uniject/PATH) with the same content like Lunelle is currently being developed (Fig. 2).

4.1.3 Contraceptive Patch

• Update

Evra (Ortho-McNeil), a contraceptive patch releasing 150 µg norelgestromin and 20 µg ethinylestradiol daily,

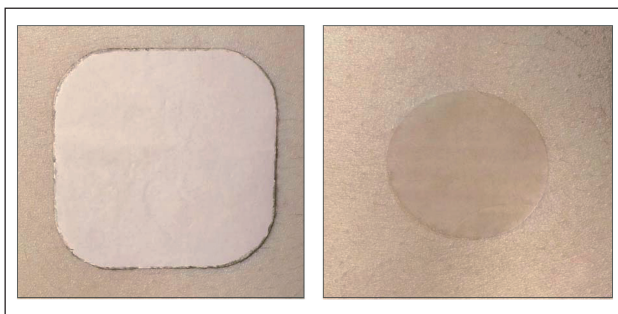


Figure 3: Contraceptive patches: Left: Evra (Ortho-McNeil). Right: Fidencia (Bayer-Schering-Pharma). Reprint with permission from Bayer-Schering-Pharma

was first approved by the FDA in 2001 (Fig. 3). The patch is applied weekly for three consecutive weeks and followed by one week without patch. The FDA approved updated labelling 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 using Evra are exposed to about 60 % more total estrogen in their blood than when taking a typical birth control pill containing 35 µg of estrogen (FDA Updates Labeling for Ortho Evra Contraceptive Patch 2005). In their Cochrane analysis, Gallo et al [50] 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 resulted in similar pregnancy rates. One trial found that patch users were more likely than oral contraceptive users to discontinue early in 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 such as 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 within the next years (Fig. 3).

The Population Council is investigating a nestorone patch for female contraception.

• Internet Links

- FDA Updates Labeling for Ortho Evra Contraceptive Patch (2005)
<http://www.fda.gov/bbs/topics/news/2005/NEW01262.html>

4.1.4 Vaginal Ring

• Update

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

Several rings have been developed in the past (levonorgestrel ring by the WHO). The Population Council has developed two vaginal rings that release natural progesterone: one for contraception during lactation called Progering® and one for hormone supplementation during

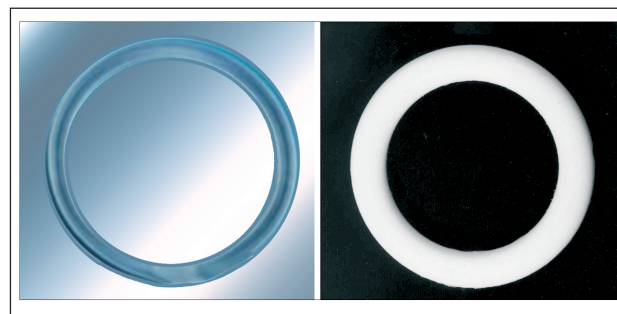


Figure 4: Left: NuvaRing® (Organon). Reprint with permission. Right: Nestorone® vaginal ring. Reprint with permission: photo of Nestorone® Vaginal Ring © 2007, The Population Council, Inc.

in vitro fertilization called Fertiring®. These rings are approved and licensed for distribution in Chile and Peru.

Finally, so far only the Nuva Ring® (Organon) (releasing 15 µg ethinylestradiol and 120 µg etonogestrel) is available in most countries of the world and highly accepted (Fig. 4).

• Trends

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

Clinical trials of a vaginal ring releasing 150 µg of nesterone (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). Nesterone is a potent, non-androgenic, 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 nesterone 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 long-acting contraceptive device, but, unlike other long-term 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 or 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>

4.2. 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

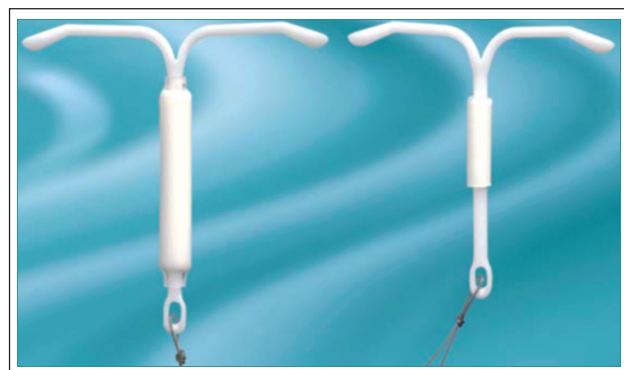


Figure 5: Levonorgestrel-releasing intrauterine systems: Left: Mirena®; Right: "Small Mirena®". Reprint with permission from Bayer-Schering-Pharma

methods (diaphragm, portio caps), spermicides, behavioural methods and surgical methods (tubal ligation). Immunocontraceptive methods focusing on surface antigens of the oocyte and sperm antigens are being tested in preclinical studies.

4.2.1 Intrauterine Devices (IUD)

• Update

The first generation of IUDs consisted of inert plastic material. The second generation were medicated IUDs, loaded either with copper or progestins. The most commonly used intrauterine devices (or coils) are made 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. Nova-T, Multiload 375). The primary mechanism of contraceptive action of copper IUDs is believed to be a pre-fertilization effect, interfering with the passage of sperm through the uterus but there is some evidence suggesting that there could also be a post-fertilization effect. Whereas the e. g. Multiload 375 and Nova-T 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.

In a Cochrane analysis, Kulier et al [51] showed that devices containing higher doses of copper are more effective in preventing pregnancies 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® (Bayer-Schering-Pharma) 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 amenorrhoea during the first 5 years of Mirena® use and up to 60 % when using the second Mirena®.

Frameless IUDs: the frameless copper-releasing GyneFix is still not widely used. In a Cochrane analysis, O'Brien and Marfleet [52] 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 determine whether the frameless IUDs could benefit women who have not had children.

• Trends

Six copper IUDs with modification in shape are: CuSafe 300, Fincoid-350, Gynefix®, Intracervical Fixing Device, Sof-T, Multiload Mark II. Other new intrauterine devices under development are: Swing: copper-releasing with coil stem; IUD releasing a progesterone receptor modulator (CDB-2914); Copper 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 IUD is also under way.

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

4.2.2 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. Diaphragms require individual fitting for each user in a clinic. During fitting, a fitting ring is inserted into the vagina. The largest ring that fits comfortably is usually the one chosen. Diaphragms can be inserted up to 2 hours before sex because spermicide is 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 55–95 mm in 5-mm intervals, Practice Diaphragm). Furthermore, there are non-latex diaphragms such as Milex Silicone Diaphragm Omniflex, Milex Silicone Diaphragm Arcing Style in sizes from 60–90 mm in 5-mm intervals.

In a Cochrane analysis, Cook et al [53] found that there is not enough evidence about the effects of using a diaphragm without a spermicide, but it may increase unwanted pregnancies.



Figure 6: New diaphragms and cervical caps: **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.

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, re-usable, made of medical-grade 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 in that it comes in one size only (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.

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

A new model is the **FemCap**, made of a non-allergenic, 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 [54] found that the Prentif Cap worked as well as the diaphragm in preventing 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.

• Internet Links

– Contraceptive Methods: Female Barrier Methods
http://www.rho.org/html/cont-female_barriers.htm

4.2.3 Hormonal Implants (Tab. 1)

• Update

An implant is a small flexible rod or a capsule placed directly under the skin in the upper arm. The Population Council, a non-profit organization located in New York, began researching subdermal contraceptive implants in

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
Nestron	Elcometrine	1 capsule	6 months
Nestron	Elcometrine	1 rod	2 years
Norgestrol	Unilant or Surplant	1 rod	1 year

*) **Norplant** distribution in the United States ended in 2002.

1966. Progestational agents include megestrol acetate, norethindrone, norgestrinone and levonorgestrel. The FDA approved subdermal contraceptive implants in 1990.

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

Jadelle: Jadelle contains two flexible, silicone-based polymer rods that are 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 FDA for use up to 5 years. Jadelle is registered in more than 25 countries.

Implanon: one rod contains 68 mg of etonogestrel and is used for up to 3 years. Implanon is available in many countries of the world (Organon). 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 its removal [55].

(Author's comment: if you are experienced in Implanon insertion and do it correctly subdermal, you will face no removal problems) (see also [56]).

In a Cochrane analysis, Power et al [57] found that all identified trials compared different types of contraceptive implants. No trials were found that compared implants to other contraceptive methods. All 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 compared to women in developing countries. The most commonly reported side effect was irregular vaginal bleeding. Bleeding with all implants became less frequent over 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.

(Author's comment: This analysis needs to be updated.)

• Trends

A single-rod subdermal implant, the **Nestorone®** implant, for female contraception, has been approved in Brazil by the Population Council.

One single-rod implant (Uniplant) uses nomegestrol acetate, another uses the progestin ST-1435. New biodegradable implants (capsules or rods) and implants with new steroids have been under investigation for years.

4.2.4 Depot Injectables

• Update

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

Depot medroxyprogesterone acetate leads to a decrease of mineral bone density in women of all ages in the reproductive phase. In adult women, bone mass can be recovered when women stop using DMPA and their estrogen levels are restored. However, concerns have been raised that DMPA in adolescent patients may have an adverse effect on bone growth because these patients have not attained maximal bone mass.
(http://www.findarticles.com/p/articles/mi_m3225/is_8_72/ai_n15863456)

In a Cochrane analysis, Draper et al [58] 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. Data were inadequate 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.

• 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, polylactidecoglycolide. Depending on 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 medroxyprogesterone acetate (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)

4.2.5 Natural Family Planning

• Update

Recently, interest in natural family planning methods has seen a modest resurgence. Modern techniques use evaluation of both cervical mucus and basal body temperature to determine the fertile time of the cycle.

Fertility awareness-based methods of family planning attempt to identify the fertile days of a woman's menstrual cycle. The goal is to avoid sexual intercourse (or use of a barrier contraceptive, like a condom, or withdrawal) on the days when she might get pregnant. Couples report that advantages include the lack of side effects, perceived

greater safety than with hormonal contraception or intrauterine devices, and low costs. On the other hand, couples note that disadvantages include trouble learning the method, difficulty in using it, and the challenge of timing intercourse [59].

The standard day method is based on abstinence/protection from cycle days 8 to 19. The "two-day" method is based on cervical mucus observation.

Natural family planning is a good choice for highly motivated patients who have religious reservations against other forms of contraception or for those who want to use a "natural" method.

Grimes et al [59] did a Cochrane analysis on fertility awareness-based methods for contraception and found that, because of poor research methods, the comparative effectiveness of fertility awareness-based methods for contraception is unknown. This review sought to identify all randomized controlled trials studying one or more fertility awareness-based methods used for contraception. Three trials were found, one from Colombia and two from Los Angeles, CA. The trials revealed difficult recruitment of couples, high drop-out rates and poor research methods. Because of these problems, the trials cannot compare how well fertility awareness-based methods work.

• 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.

4.2.6 Spermicides

• Update

Spermicides are chemical products inserted into 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 FDA 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 antimicrobial 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. Buffer-Gel and Acidform.
- Surfactant products: e. g. acylcarnitine analogues, C31G.
- Products which block attachment of HIV to target cells and sperm-zona pellucida fusion: e. g. naphthyl urea derivatives.
- The Population Council is investigating **Carraguard®**, a vaginal microbicide for protection against HIV transmission, in clinical trials.

Algae gel against HIV: new gels derived from algae are being investigated in clinical trials in view of a possible HIV protection. An efficiency of 95 % has been claimed in preliminary lab tests. The inventor hopes the gel – one of a new generation of microbicides seen as key to prevent HIV infection in women – will be available by 2014. (<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 was recently stopped.

"Molecular condom": 'smart' vaginal drug delivery system (DDS), called a 'molecular condom'. Composed of a biologically responsive polymer liquid at room temperature (for improved coating of tissue), it turns into a gel 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/cont-spermicides.html>

4.2.7 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 F-5 Gel®. The individu-

ally wrapped sponge is ready to use and is designed with die-cut 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 US. In 1994, the manufacturer halted production of the device because of production problems. The product line was bought by Allendale Pharmaceuticals in 1995, who have been trying to reintroduce production for the US market. In June 2005, the Today Sponge returned to stores in the US. The Today Sponge is also available in Canada.

4.2.8 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, FC2, V-Amour are the names of the new products.

Femidom (made of polyurethane) has been available for several years. FC2 (made of nitrile), V-Amour (made of latex) are the names of the new products on the market.

4.2.9 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 relationship are sterilized) [60].

For many women in developing countries, sterilisation is the first-choice method of contraception they use. Tubal sterilisation is the most common method of contraception used in the US. More than 10 million women in the US are sterilised. The Centers for Disease Control and Prevention reported cumulative pregnancy rates for surgical sterilisation in the US of 5.5 pregnancies/1000 women at 1 year, 13/1000 at 5 years, and 18.5/1000 at 10 years. This means that almost two pregnancies per 100 women by 10 years occur although this risk varies by method and timing of sterilisation, age, race and ethnicity [56].

Tubal ligation or sterilisation (tying the tubes) is a common method of fertility regulation. It is usually done by using one of the following methods: mini-laparotomy (through a small cut in the abdomen), laparoscopy ("key-hole" surgery – through a tube inserted through the umbilicus [belly button] or a very small cut) or culdoscopy (using a tube, but through the vagina) [61].

In a Cochrane analysis, Nardin et al [61] 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 as 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 [62] analysed mini-laparotomy and endoscopic techniques for tubal sterilisation. The review found that, overall, laparoscopy was associated with fewer complications than mini-laparotomy but it requires more sophisticated expensive equipment and greater skills. Culdoscopy has higher rates of complications.

Quinacrine: for more than 20 years, chemical sterilisation with quinacrine has been evaluated in clinical trials: the polymerising agent, quinacrine, leads to the occlusion of the fallopian tube.

New techniques for female sterilization are:

Essure: hysteroscopic sterilisation by insertion of titanium in the proximal part of the fallopian tube (Fig. 7). 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 [57].

Adiana: heating the inner lining of the fallopian tube by radiofrequency and insertion of a soft, inert polymer matrix via a delivery catheter (Fig. 7).

Ovabloc: sterilisation method for women by inserting a rubber plug into both fallopian tubes (Fig. 7).

• 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 while 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=S0042-96862003000200013&script=sci_arttext
- Reproductivehealth/UnintendedPregnancy/Sterilization
<http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/Sterilization.htm>

4.2.10 Immunocontraception

• Update

Immunocontraception is a non-hormonal, non-steroidal 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 fertilisation 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 [63, 64].

• Trends

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

4.2.11 Antiprogestins

According to the WHO [1], anti-progestins for contraception can be used in different regimens:

- Sequential regimens:
 - Mifepristone + Norethisterone
 - Mifepristone + Medroxyprogesterone acetate
 - Mifepristone (days 1–15) + Norgestrel 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

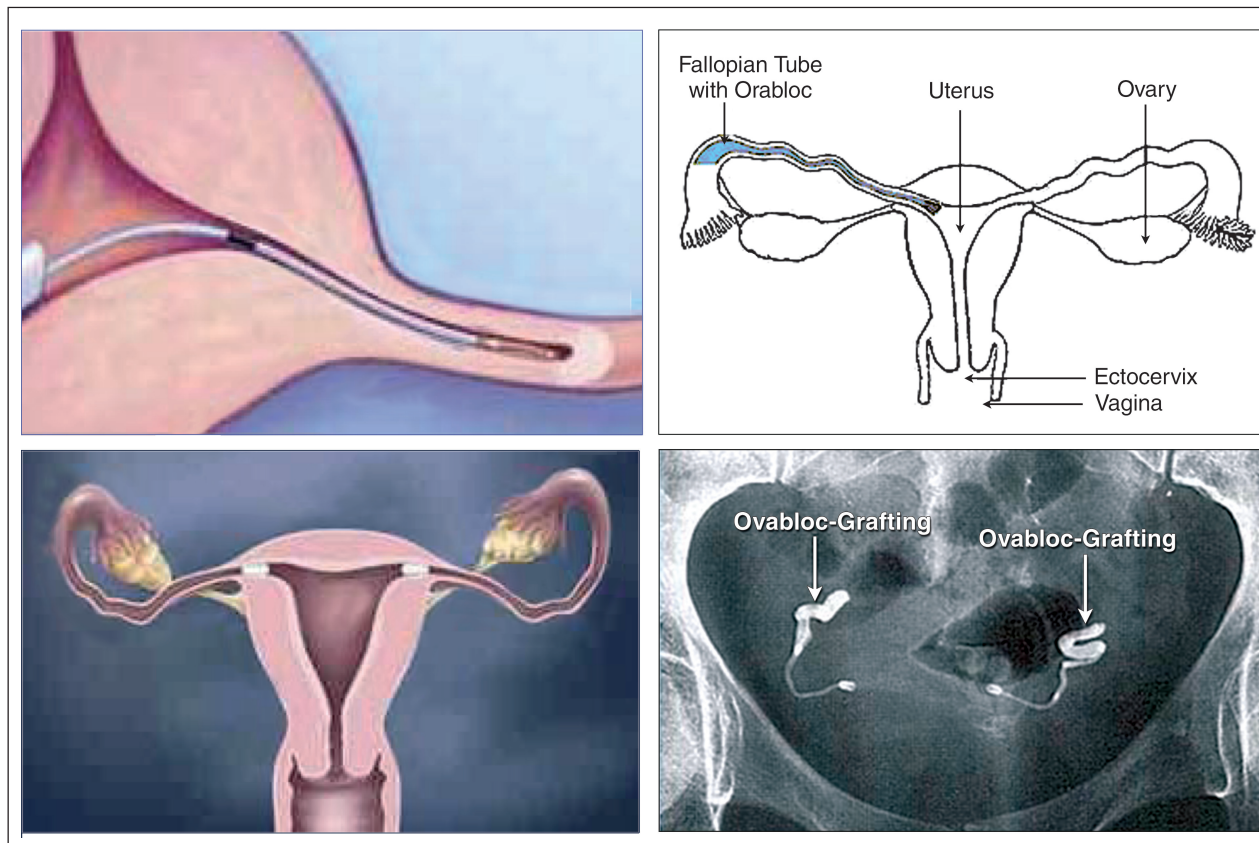


Figure 7: New female sterilisation techniques. **Left: Upper figure:** Essure; reprint with permission from Conceptus Inc. **Lower figure:** Adiana (www.thewelltimedperiod.blogspot.com); reprint with permission. **Right:** Ovabloc (www.ovabloc.com/ovabloc-de/eingriff.html); reprint with permission.

4.3 Implantation Inhibition

4.3.1 Postcoital Contraceptive Steroids

• Update

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

Post-coital pills are available worldwide, in some countries as prescription-free over-the-counter pills. A one-time 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. The WHO has undertaken research in this field 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. Recent efforts to improve the use of emergency contraceptive pills include the testing of more simple pill regimens in multicentre studies in 16 countries around the world. Research is being carried out on both levonorgestrel and mifepristone pills, including studies on: safety and efficacy of a single-dose regimen of levonorgestrel (1.5 mg) compared to a two-dose regimen (0.75 mg taken 12 hours apart), and to mifepristone (10 mg); the possibility of increasing the 12-hour interval for levonorgestrel pills to 24 hours; safety and efficacy of mifepristone (both 10 and 25 mg) [65–68].

In a Cochrane analysis, Cheng et al [69] analysed interventions for emergency contraception. Levonorgestrel and mifepristone are very effective with few adverse effects, and are preferred to oestrogen 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 maintained 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 copper-bearing 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 IUDs for use in emergency contraception. Further initiatives investigate the possible mechanisms of action of emergency contraceptives.

Selective modulators of progesterone receptors (SPRMs), also known as antiprogestins, seem very promising in emergency contraception since they are longer efficient than levonorgestrel (120 h), and because they have a dual effect: their administration prevents the LH surge and also alters implantation by their effect on the endometrium. Studies using low doses of RU 486 (mifepristone) or HRA 2914 (ulipristal or Ella®) show an improved rate of efficacy over LNG. These products will probably be available on the market in 2008.

• Internet Links

- WHO information sheet for emergency contraception http://www.who.int/reproductive-health/family_planning/docs/ec_factsheet.pdf

4.3.2 Immunocontraception

Immunocontraception focuses 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 fertilisation and which is necessary for the maintenance of pregnancy. As a 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 six months or more of protection against pregnancy following a single injection, without inducing 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: the 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, Gene-Based Approaches Promise Dramatic Change in Contraception <http://www.infoforhealth.org/pr/m19/supplements/novel.shtml>

4.3.3 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.

5. Male Contraception

Male contraception is based on inhibition of sperm production, inhibition of the maturation of spermatozoa, blockage of sperm transport, prevention of sperm deposition, modification of sperm function and prevention of fertilization.

5.1 Inhibition of Spermatogenesis

• Update

No male contraceptive inhibiting spermatogenesis is available on the market.

An overview of 30 clinical studies searching for a steroidal male contraceptive – using androgens or andro-

gen-progestin combinations – published between 1990 and 2005 has been published by Liu et al [70].

According to a WHO release, a large clinical trial on the safety and efficacy of testosterone undecanoate, an injectable preparation that has shown good results in sperm suppression in earlier studies, is under way in China. Additional encouraging data are available from a pilot study combining this testosterone formulation with the injectable progestogen, depot medroxyprogesterone acetate (DMPA). Additional multi-national clinical trials on similar hormonal combinations are planned.

Grimes et al [71] found in a Cochrane analysis 30 trials that met the inclusion criteria. To date, the proportion of men who achieved azoospermia has varied widely in reports. A few important differences emerged from these trials: levonorgestrel implants (160 µg per day) combined with injectable testosterone enanthate (TE) were more effective than levonorgestrel 125 µg daily combined with testosterone patches; levonorgestrel 500 µg daily improved the effectiveness of TE 100 mg injected weekly; desogestrel 150 µg was less effective than desogestrel 300 µg (with testosterone pellets); testosterone undecanoate (TU) 500 mg was less likely to produce azoospermia than TU 1000 mg (with levonorgestrel implants); norethisterone enanthate 200 mg with TU 1000 mg led to more azoospermia when given every 8 weeks versus 12 weeks. Four implants of 7- α -methyl-19-nortestosterone (MENT) were more effective than two MENT implants.

Several trials showed promising efficacy in terms of percentages with azoospermia. Three examined desogestrel and testosterone preparations or etonogestrel (metabolite of desogestrel) and testosterone, and two examined levonorgestrel and testosterone.

Most trials were small pilot studies investigating different hormone treatments. Larger trials with better methods are needed to test good leads in this area.

Another possible approach is the use of GnRH analogues and, in addition, testosterone supplementation (oral, transdermal or by injectables).

• Trends

According to a WHO statement, methods to suppress sperm production (according to [1]) include:

- Hormonal
 - testosterone esters
 - progestins or GnRH analogues + testosterone
- Immunological, based on antibodies against
 - GnRH, LH, FSH and their receptors

Adjudin®: the Population Council is conducting basic research that may pave the way for nonhormonal contraceptives for men. Council researchers have identified a compound, Adjudin®, that has potent, reversible anti-spermatogenic effects in animal studies. They are exploring delivery systems for this product.

Recommendations for regulatory approval for hormonal male contraception were summarized at the 10th Summit Meeting on Hormonal Male Contraception [72].

Recently, Bayer-Schering-Pharma and Organon stopped research on and development of a hormonal male contraceptive. So far, the combination of desogestrel and long-acting testosterone preparations has been successfully tested in phase-II clinical trials with about 300 participants in six European countries but a much larger group of men would need to be tested in phase-III trials for

regulatory approval (<http://www.rsc.org/chemistryworld/News/2007/June/22060701.asp>).

• Internet Links

- Male hormonal contraceptives. Homepage of www.malecontraceptives.org
<http://www.malecontraceptives.org/methods/hormonal.php>
- Witchall (2005)
<http://www.zeit.de/zeit-wissen/2005/02/verhuetungenglisch5.2>

5.2 Inhibition of Spermatozoa Maturation

Interference with spermatozoa maturation due to anti-androgens or alpha-chlorohydrin. Some experimental studies have been done or are ongoing – but until now no good approach is available.

5.3 Inhibition of Sperm Transport

5.3.1 Condoms

• Update

Inhibition of sperm transport is classically interrupted by use of condoms, additionally providing some protection against sexually transmitted diseases (65 million of 300 million US Americans are suffering from 1 of 25 incurable sexually transmitted diseases) (increasing incidence of HIV and AIDS worldwide). Different sizes of condoms, various strengths and various thicknesses of the material, different materials (latex and non-latex, if people are allergic or sensitive to latex), with and without lubricants, with flavour and different colours and shapes are available. Lubricants or special hydrogels can be applied, lubricants containing no mineral oil should be used.

A Cochrane analysis done by Gallo et al [73] deals with non-latex versus latex male condoms for contraception. The main issues were effect on birth control, whether the condom broke or slipped, and which condoms people liked. The eZ-on condom did not prevent pregnancy as well as latex condoms. The Avanti and the Standard Tactylon condoms were similar to latex condoms for birth control. Non-latex condoms broke more often than latex condoms. However, many people liked non-latex condoms better. They may be useful for people who are allergic or sensitive to latex.

• Trends

Condoms coated with spermicidal and microbicidal activities.

New male condoms according to the WHO (according to [1]) are:

- Polyurethane: Avanti, eZ.on, Supra
- Styrene-based plastic: Tactylon, Unique, Unisex

Recent new developments are the “invisible condom” and the “spray-on condom”.

5.3.2 Sterilisation Techniques

Methods for male sterilisation can be classified according to the WHO [1]:

- No-scalpel vasectomy
- Fascial interposition
- Percutaneous vas occlusion
 - Permanent, with sclerosing agents: e. g. methylcyanoacrylate, polyurethane
 - Reversible, with non-sclerosing agents: e. g. silicone plugs or resins: e. g. maleic anhydride/styrene

• Update

Male sterilisation still represents an important family-planning method (42 million men living today have undergone vasectomy) (WHO Research on Reproductive Health 2000–2001). Vasectomy tends to be more popular in industrialized countries – New Zealand and the UK top the vasectomy league with a prevalence of 18 % among men who are married or in union, but it came as a surprise to learn that the figure is as high as 8 % for Bhutan and 5.4 % for Nepal [60].

A vasectomy can be performed via surgical and non-surgical techniques (Figs. 8, 9) [74].

Surgical techniques [75]: usually, surgery involves cutting the skin of the scrotum with a scalpel, isolation of the vas out of the scrotum, occlusion of the vas using suture material (vas ligation) (with and without folding back; with and without fascial interposition; with and without leaving the testicular end) or metal clips (2 or 4); cautery (thermal, electrocautery). Current evidence supports no-scalpel vasectomy as the safest surgical approach to isolate the vas when performing vasectomy. Adding fascial interposition increases effectiveness beyond ligation and excision alone. Occlusive effectiveness appears to be further improved by combining interposition with cautery.

Cook et al [76] made a Cochrane analysis for vasectomy methods and found six studies. One trial compared closing the vas with clips versus the usual cutting of the vas. The groups did not differ in reaching a low sperm count or in side effects. Three trials looked at flushing fluids through the vas: two compared vasectomy with water flushing versus vasectomy alone, and one compared using water versus euflavine (which kills sperm). None found a difference between the groups in time with regard to low sperm count. However, one trial found that the usual number of ejaculations before low sperm count was lower with euflavine than with water. One trial comparing vasectomy with and without fascial interposition was a large high-quality study. The fascial interposition group was less likely to have vasectomy failure. However, surgery was more difficult. Side effects were about the same in the two groups. Finally, one trial looked at a device placed into the vas versus vasectomy without a scalpel. The intra-vas device did not work as well for reaching a low sperm count but more men liked the method. Most of the studies that looked at vasectomy methods were small, not done well or had poor reports. Therefore, the authors cannot conclude if the methods work well, are safe or are liked by men.

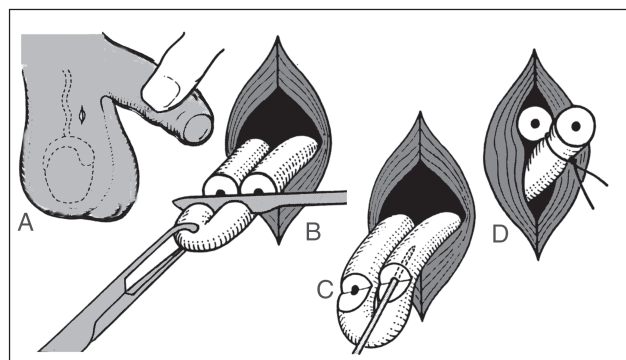


Figure 8: Vasectomy: resection and electrocauterisation (Reprint from [74]).

A newer technique uses a sharp instrument to puncture the skin instead. The intent is to have fewer problems with bleeding, bruising and infection. In a Cochrane analysis, Cook et al [66] compared scalpel versus no-scalpel incision for vasectomy. They found two trials that looked at the no-scalpel approach to the vas. The trials showed somewhat different results. The larger trial showed that the no-scalpel method led to less bleeding, infection and pain during and after the procedure. The no-scalpel approach required less time for the operation and had a faster return to sexual activity. The smaller study did not show these differences. However, the study may have been too small and many men dropped out. The two methods did not differ in the numbers of men who became sterile.

Non-surgical techniques: see trends.

• Trends

Promising areas of non-hormonal male contraception: vas-based methods (no-scalpel vasectomy, chemical injection, injectable plugs, the Intra Vas Device (previously known as the „Shug“) and SMA (styrene malic anhydride) as well as heat methods (simple wet heat, artificial cryptorchidism, polyester suspensories and ultrasound) (Fig. 10).

New vas-occlusive devices: the Intra Vas Device (IVD) consists of a tubular silicone plug that is inserted into the lumen of the vas deferens to block the flow of semen. IVD implantation does not require the need to sever or permanently damage the vas deferens as in ligation/excision, clip devices, cautery techniques or fascial interposition [77].

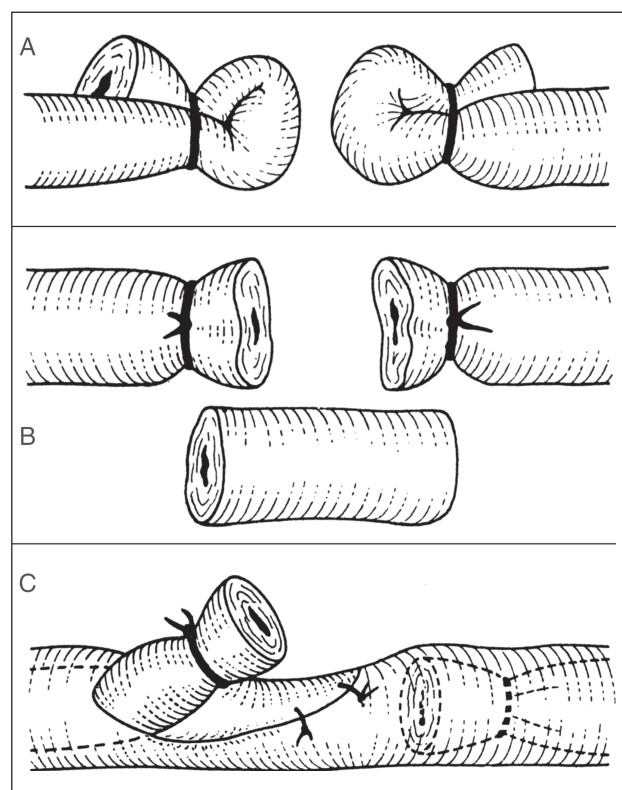


Figure 9: Vasectomy: resection and ligation: A) resection, folding and ligation; B) resection and ligation; C) resection and interfascial positioning. (Reprint from [74]).

• Internet Links

- FHI – Expert Consultation on Vasectomy (2003)
<http://www.fhi.org/en/RH/Pubs/booksReports/vasconrpt.htm>

5.4 Male Immunocontraception

Male immunocontraception focuses on antigens at the surface of the spermatocyte necessary for capacitation (e. g. protein Izumo important for attachment of the sperm head at the surface of the oocyte, proteins responsible for chemotaxis leading the spermatozoa the correct way to the oocyte), interaction with spermatogenesis at a lower level of development (e. g. spermatogonia) [64, 78–82].

Chemical sterilisation in males by use of SMA (styrol-maleinacid-anhydrid) inside the vas deferens: SMA is attached to the internal wall of the vas deferens and remains there up to 10 years, inactivating spermatozoa by changing the electrical potential and pH value of the environment.

• Internet Links

- Population reports (2007): family planning: a global handbook for providers. Chapter 12: vasectomy
http://www.infoforhealth.org/globalhandbook/book/fph_chapter12/index.shtml

6. 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.

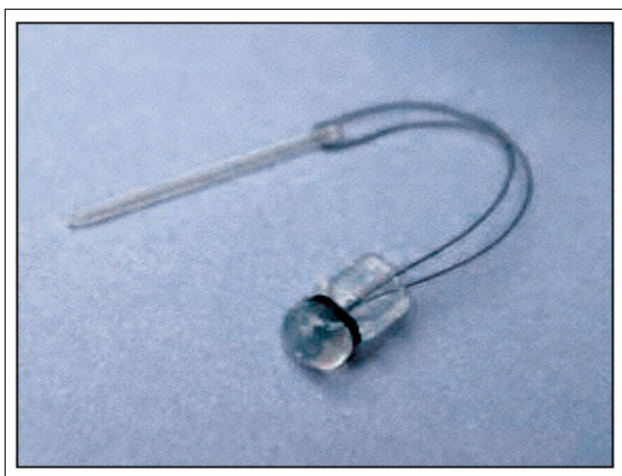


Figure 10: "Intra Vas Device" shown with anchor thread and keeper; keeper is removed after insertion. Reprint with permission from Male Contraception Information Project.

Predicted developments (modified according to [83], WHO [1]):

Within five years: new delivery systems of conventional contraceptives such as vaginal rings, transdermal patches and gels. Contraceptives that also protect against sexually transmitted diseases. Furthermore, new oral contraceptives with new progestins in combination with estradiol or estradiolesters.

Short term (< 10 years): "once-a-month" pill that inhibits implantation; antiprogestogens used for 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 sperm-binding 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; eba (endometrial bleeding-associated factor)
- Anti-angiogenic agents (magainin analogues (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).

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:

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. Oral contraceptive prescribing: should body weight influence choice of pill? Questions and Answers with Associate Editor Mitchell D. Creinin, MD. *The Contraception Report* 14; 4: 11–2, 15.
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. Singletary SE. Rating the risk factors for breast cancer. *Ann Surg* 2003; 237: 474–82.
12. 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.
13. 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.
14. 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.
15. Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, Andriulis 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.
16. Paul CD, Skegg DCG, Spears GFS, Kaldor JM. Oral contraceptives and breast cancer: A national study. *Br Med J* 1986; 293: 723–5.
17. Oral-contraceptive use and the risk of breast cancer. 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* 1986; 315: 405–11.
18. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer in young women and use of oral contraceptives: Possible effect of formulation and age at use. *Lancet* 1983; 22: 926–9.
19. Miller DR, Rosenberg L, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer risk in relation to early oral contraceptive use. *Obstet Gynecol* 1986; 68: 863–8.
20. Olsson H, Olsson ML, Moeller TR, Ranstam J, Holm P. Oral contraceptive use and breast cancer in young women in Sweden. *Lancet* 1985; 1: 748–9.
21. McPherson K, Vessey MP, Neil A, Doll R, Jones L, Roberts M. Early oral contraceptive use and breast cancer: results of another case-control study. *Br J Cancer* 1987; 56: 653–60.
22. Huggins GR, Zucker PF. Oral contraceptives and neoplasia: 1987 update. *Fertil Steril* 1987; 47: 733–61.
23. McPherson K, Drife JO. The pill and breast cancer: why the uncertainty? *Br Med J* 1986; 293: 709–10.
24. Schlesselman JJ, Stadel BV, Murray P, Lai S. Breast cancer in relation to early use of oral contraceptives. No evidence of a latent effect. *JAMA* 1988; 259: 1828–33.
25. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, Stampfer MJ, Willett W, Peto R. A case-control study of oral contraceptive use and breast cancer. *J Natl Cancer Inst* 1984; 72: 39–42.
26. Wingo PA, Harland A, Marchbanks PA, Whiteman MA, Hsia J, Mandel MG, Peterson HB, Ory HW. Oral contraceptives and the risk of death from breast cancer. *Obstet Gynecol* 2007; 110: 793–8.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, Ben-Baruch G, Fishman A, Menczer J, Ebbert SM, Tucker MA, Wacholder S, Struwing 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.
34. Franceschi S. The IARC commitment to cancer prevention: the example of papillomavirus and cervical cancer. *Recent Results Cancer Res* 2005; 166: 277–97.
35. 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.
36. 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.
37. 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.
38. 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.
39. Yu MC, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* 2004; 127 (Suppl 1): 72–8.
40. 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.
41. Meirik O, Farley TMM. Risk of cancer and the oral contraceptive pill. *BMJ* 2007; 335: 621–2.
42. Gallo MF, Grimes DA, Schulz KF, d'Arcangues C, Lopez LM. Combination injectable contraceptives for contraception. *Cochrane Database Syst Rev* 2005; (3): CD004568.
43. 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.
44. 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.
45. 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.

46. 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.
47. Richards JS, Russell DL, Ochsner S, Espey LL. Ovulation: new dimensions and new regulators of the inflammatory-like response. *Annu Rev Physiol* 2002; 64: 69–92.
48. 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.
49. 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.
50. Gallo MF, Grimes DA, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2003; (1): CD003552.
51. 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.
52. O'Brien PA, Marfleet C. Frameless versus classical intrauterine device for contraception. *Cochrane Database Syst Rev* 2005; (1): CD003282.
53. Cook L, Nanda K, Grimes D. Diaphragm versus diaphragm with spermicides for contraception. *Cochrane Database Syst Rev* 2003; (1): CD002031.
54. Gallo MF, Grimes DA, Schulz KF. Cervical cap versus diaphragm for contraception. *Cochrane Database Syst Rev* 2002; (4): CD003551.
55. Arzneimittelkommission der deutschen Ärzteschaft. „Aus der UAW-Datenbank“: Misslungene Explantation des implantierbaren Kontrazeptivums Implanon®. *Dt Ärzteblatt* 2006; 103: A-1771, B-1519, C-1471.
56. Jacobstein R. Long-acting and permanent contraception: an international development, service delivery perspective. *J Midwifery Womens Health* 2007; 52: 361–7.
57. 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.
58. 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.
59. Grimes DA, Gallo MF, Halpern V, Nanda K, Schulz KF. Fertility awareness-based methods for contraception. *Cochrane Database Syst Rev* 2004; (4): CD004860.
60. Scott A, Glasier A. Contraceptive sterilization: global issues and trends. *Bull World Health Organ* 2003; 81: 146.
61. 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.
62. Kulier R, Boulvain M, Walker D, De Candallo G, Campana A. Minilaparotomy and endoscopic techniques for tubal sterilisation. *Cochrane Database Syst Rev* 2002; (3): CD001328. Update in: *Cochrane Database Syst Rev* 2004; (3): CD001328.
63. Naz RK, Zhu X, Kadam AL. Identification of human sperm peptide sequence involved in egg binding for immunocontraception. *Biol Reprod* 2000; 62: 318–24.
64. Naz RK, Gupta SK, Gupta JC, Vyas HK, Talwar GP. Recent advances in contraceptive vaccine development: a mini-review. *Hum Reprod* 2005; 20: 3271–83.
65. Wertheimer RE. Emergency postcoital contraception. *Am Fam Physician* 2000; 62: 2287–92.
66. Glasier A. Emergency postcoital contraception. *N Engl J Med* 1997; 337: 1058–64.
67. Comparison of three single doses of mifepristone as emergency contraception: a randomised trial. Task Force on Postovulatory Methods of Fertility Regulation. *Lancet* 1999; 353: 697–702.
68. von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bárfai G, Ng E, Gemzell-Danielsson K, Oyunbileg A, Wu S, Cheng W, Lüdicke F, Pretnar-Darovec A, Kirkman R, Mittal S, Khomassuridze A, Apter D, Peregoudov A; WHO Research Group on Post-ovulatory Methods of Fertility Regulation. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; 360: 1803–10.
69. Cheng L, Gülmezoglu AM, Oel CJ, Piaggio G, Ezcurra E, Look PF. Interventions for emergency contraception. *Cochrane Database Syst Rev* 2004; (3): CD001324.
70. Liu PY, Swerdloff RS, Christenson PD, Handelsman DJ, Wang C; Hormonal Male Contraception Summit Group. Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. *Lancet* 2006; 367: 1412–20.
71. Grimes DA, Lopez LM, Gallo MF, Halpern V, Nanda K, Schulz KF. Steroid hormones for contraception in men. *Cochrane Database Syst Rev* 2007; (2): CD004316.
72. Aaltonen P, Amory JK, Anderson RA, Behre HM, Bialy G, Blithe D, Bone W, Bremner WJ, Colvard D, Cooper TG, Elliesen J, Gabelnick HL, Gu YQ, Handelsman DJ, Johansson EA, Kersemaekers W, Liu P, MacKay T, Matlin S, Mbizvo M, McLachlan RI, Meriggiola MC, Mletzko S, Mommers E, Muermans H, Nieschlag E, Odland V, Page ST, Radlmaier A, Sitruk-Ware R, Swerdloff R, Wang C, Wu F, Zitzmann M. 10th Summit Meeting consensus: recommendations for regulatory approval for hormonal male contraception. *J Androl* 2007; 28: 362–3.
73. Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male condoms for contraception. *Cochrane Database Syst Rev* 2006; (1): CD003550.
74. Weisak WH. Vasektomie – aktueller Stand. *J Reproduktionsmed Endokrinol* 2004; 1: 222–7.
75. Labrecque M, Pile J, Sokal D, Kaza RC, Rahman M, Bodh SS, Bhattarai J, Bhatt GD, Vaidya TM. Vasectomy surgical techniques in South and South East Asia. *BMC Urol* 2005; 5: 10.
76. Cook LA, Van Vliet H, Lopez LM, Pun A, Gallo MF. Vasectomy occlusion techniques for male sterilization. *Cochrane Database Syst Rev* 2007; (2): CD003991.
77. Cook LA, Pun A, van Vliet H, Gallo MF, Lopez LM. Scalpel versus no-scalpel incision for vasectomy. *Cochrane Database Syst Rev* 2007; (2): CD004112.
78. Edwards RG. Immunological control of fertility of female mice. *Nature* 1964; 203: 50–3.
79. Naz RK, Vaneck CM. Testis-specific proteins and their role in contraceptive vaccine development. *Front Biosci* 1998; 3: 39–48.
80. Kuma TCA. Development of immunocontraceptives: an introduction. *Human Reproduction Update* 1997; 3: 299–300.
81. O'Rand MG, Widgren EE, Sivashanmugam P, Richardson RT, Hall SH, French FS, VandeVoort CA, Ramachandra SG, Ramesh V, Jagannadha Rao A. Reversible immunocontraception in male monkeys immunized with eppin. *Science* 2004; 306: 1189–90.
82. Nieschlag E, Henke A. Hopes for male contraception. *Lancet* 2005; 365: 554–6.
83. Baird DT. Overview of advances in contraception. *Br Med Bull* 2000; 56: 704–16.

Further References:

- Aitken RJ, Paterson M, van Duin M. The potential of the zona pellucida as a target for immunocontraception. *Am J Reprod Immunol* 1996; 35: 175–80.
- Aitken RJ. Immunocontraceptive vaccines for human use. *J Reprod Immunol* 2002; 57: 273.
- Baird DT, Glasier AF. Science, medicine, and the future. *BMJ* 1999; 319: 969–72.
- Brinton LA, Daling JR, Liff JM, Schoenberg JB, Malone KE, Stanford JL, Coates RJ, Gammon MD, Hanson L, Hoover RN. Oral contraceptives and breast cancer risk among younger women. *J Natl Cancer Inst* 1995; 87: 827–35.
- Cameron ST, Thong KJ, Baird DT. Effect of low dose mifepristone on the ovarian cycle and on the dynamics of follicle growth. *Clin Endocrinol* 1995; 43: 407–14.
- Chwalisz K, Brenner RM, Fuhrmann UU, Hess-Stump H, Elger W. Antiproliferative effects of progesterone antagonists and progesterone receptor modulators on the endometrium. *Steroids* 2000; 65: 741–51.
- Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. *Hum Reprod* 1993; 8: 201–7.
- Emons G, Fleckenstein G, Hinney B, Huschmand A, Heyl W. Hormonal interactions in endometrial cancer. *Endocr Relat Cancer* 2000; 7: 27–42.

- Lakha F, Ho PC, Van der Spuy ZM, Elton KDR, Glasier AF, Critchley HOD, Williams ARW, Baird DT. A novel estrogen-free oral contraceptive pill for women: multicentre, double-blind, randomized controlled trial of mifepristone and progestogen-only pill (levonorgestrel). *Hum Reprod* 2007; 22: 2428–36.
- Naz RK, Sacco A, Singh O, Pal R, Talwar GP. Development of contraceptive vaccines for humans using antigens derived from gametes (spermatozoa and zona pellucida) and hormones (human chorionic gonadotropin): current status. *Hum Reprod* 1995; 1: 1–18.
- Nieschlag E. "Sixth Summit Meeting Consensus: Recommendations for regulatory approval for hormonal male contraception." *Int J Androl* 2002; 25: 375.
- Nieschlag E, Behre HM (eds). *Andrology: Male reproductive health and dysfunction*. 2nd ed. Springer, Heidelberg, 2000.
- Jacobstein R. Long-acting and permanent contraception: an international development, service delivery perspective. *J Midwifery Womens Health* 2007; 52: 361–7.
- Scott A, Glasier A. Evidence based contraceptive choices? *Best Pract Res Clin Obstet Gynaecol* 2006; 20: 665–80.
- Swerdloff R, Steiner B, Callegari C, Bhasin S. GnRH analogues and male contraception. In: Bhasin S et al (eds). *Proceedings of the 2nd International Androgen Workshop*. Wiley-Liss, New York, 1995.
- Ulmann AJ. The development of mifepristone: a pharmaceutical drama in three acts. *J Am Med Womens Assoc* 2000; 55 (3 Suppl): 117–20.
- van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev* 2006; (3): CD002032
- von Hertzen H, Van Look PFA. Antiprogestins for contraception? *Semin Reprod Med* 2005; 23: 92–100.
- Waites GMH. Development of methods of male contraception: impact of the World Health Organization Task Force. *Fertil Steril* 2003; 80: 1–15.
- Wassarman PM. Mammalian fertilization: molecular aspects of gamete adhesion, exocytosis, and fusion. *Cell* 1999; 96: 175–83.
- Wu X, Viveiros MM, Eppig JJ, Bai Y, Fitzpatrick S, Matzuk MM. Zygote arrest 1 (Zar1) is a novel maternal-effect gene critical for the oocyte-to-embryo transition. *Nat Genet* 2003; 33: 187–91.
- Zhou CX, Zhang YL, Xiao L, Zheng M, Leung KM, Chan MY, LO PS, Tsang LL, Wong HY, Ho LS, Chung YW, Chang HC. An epididymis-specific beta-defensin is important for the initiation of sperm maturation. *Nat Cell Biol* 2004; 6: 458–64.

Further Internet Links:

- Cochrane Collaboration Topic: Fertility Regulation. New topic. Contraception related reviews. Abortion related reviews. Review of progestogens in combined oral contraceptives for contraception. <http://www.cochrane.org/reviews/en/topics/64.html>
- Emergency Contraceptive Pills: Medical and service delivery guidelines. Second Edition, 2004. International Consortium for Emergency Contraception, Washington DC, USA. http://www.cecinfo.org/publications/PDFs/resources/MedicalServiceDeliveryGuidelines_Eng.pdf
- Kuyoh MA, Toroitich-Ruto C, Grimes DA, Schulz KF, Gallo MF. Sponge versus diaphragm for contraception: a Cochrane review. <http://cat.inist.fr/?aModele=afficheN&cpsidt=14469947>
- Population reports: Family planning: a global handbook for providers. Chapter 11: female sterilization. http://www.infoforhealth.org/globalhandbook/book/fph_chapter11/index.shtml

Mitteilungen aus der Redaktion

Besuchen Sie unsere Rubrik

☒ Medizintechnik-Produkte



Neues CRT-D Implantat
Intica 7 HF-T QP von Biotronik



Artis pheno
Siemens Healthcare Diagnostics GmbH



Philips Azurion:
Innovative Bildgebungslösung

Aspirator 3
Labotect GmbH



InControl 1050
Labotect GmbH

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☒ Bestellung e-Journal-Abo

Haftungsausschluss

Die in unseren Webseiten publizierten Informationen richten sich **ausschließlich an geprüfte und autorisierte medizinische Berufsgruppen** und entbinden nicht von der ärztlichen Sorgfaltspflicht sowie von einer ausführlichen Patientenaufklärung über therapeutische Optionen und deren Wirkungen bzw. Nebenwirkungen. Die entsprechenden Angaben werden von den Autoren mit der größten Sorgfalt recherchiert und zusammengestellt. Die angegebenen Dosierungen sind im Einzelfall anhand der Fachinformationen zu überprüfen. Weder die Autoren, noch die tragenden Gesellschaften noch der Verlag übernehmen irgendwelche Haftungsansprüche.

Bitte beachten Sie auch diese Seiten:

Impressum

Disclaimers & Copyright

Datenschutzerklärung