

HTA-Report | Summary

Benefits and risks of hormonal contraception for women

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Scientific background

Background to pregnancy prevention

Conception is defined as the fusion of an egg cell with a sperm cell. Should the fertilised egg nest in the uterus, pregnancy evolves and most often results in birth. Methods which enable sexual intercourse without pregnancy, or with reduced risk of pregnancy, are defined as methods of pregnancy prevention. Currently, nearly 17.2 million women (41 % all women) in Germany are of reproductive age. A large proportion of these women use various methods of pregnancy prevention.

The methods for pregnancy prevention may be divided into methods which use hormones and those which do not. Evaluating these methods should differentiate between their perfect and typical use, which also considers possible application errors.

Pregnancy prevention methods which do not use hormones are: methods without the use of any appliances (abstinence and discontinuation of sexual intercourse), chemical contraceptives (spermicides), mechanical contraceptives (condoms, spirals, vaginal rings), surgical contraception (tubal ligation, vasectomy) as well as simultaneous combination of several methods.

Pregnancy prevention methods with the use of hormones may be divided in: combined estrogen-progestogen contraceptives (pills, skin patches, vaginal rings), progestogen-only contraceptives (pills, injections, implants, hormone spirals) and emergency contraceptives.

Pregnancy prevention methods which use hormones

Combined estrogen-progestogen and progestogen-only hormone contraceptives are used for pregnancy prevention. The estrogen compound ethinyl estradiol is applied in most combined contraceptives, in a few others mestranol or estradiol cypionat. The daily dose of estrogens in the first preparations was more than 50 µg / day and declined through further development down to 20 to 30 µg / day in current applications.

In the literature, progestogen compounds in contraceptives are often divided into three generations according to the development period (beginning of the 60s, 70s and 80s). Compounds of the first generation are norethindron, ethynodiol diacetate, lynestrenol, norethynodrel and dienogest, of the second levonorgestrel, norgestrel, and norgestrone, of the third desogestrel, norgestimate and gestodene. Further agents, such as drospirenone, cyproteron acetate and chlormadion acetate, are defined as unclassified.

Cost of hormone contraceptives

The German retail price of N2 packages (for three cycles) of oral contraceptives is approximately 21 to 37 euros, of three-month-injections 29 to 30 euros, of skin patches and of vaginal rings 38 to 40 euros. The price of hormone implants is quoted as 194 euros per three years use, for emergency contraceptives 16 to 18 euros per single use. To compare: the cost for one package of spermicide in Germany is approximately 10 to 5 euros, for one

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male condom 0.50 euros, for one female condom 5 euros, for a diaphragm 20 euros, for a cervical cap 25 euros, for a copper spiral 150 euros, for a hormone implant 300 euros, and for a hormone spiral 300 euros.

Research questions

This report addresses the following questions:

- What are the medical benefits and risks of the use of hormone contraceptives for women?
- What are the health-economics consequences of the use of hormone contraceptives?
- Which ethical implications must be noted?

Medical evaluation

Methods

The literature was searched in April 2006, beginning from 2000 in the most important medical electronic databases (MEDLINE, MEDLINE Alert, EMBASE, EMBASE Alert, SciSearch, BIOSIS, DAHTA-database, Cochrane Database of Systematic Reviews etc.). Further systematic reviews were identified through searches in publications' reference lists and expert contacts.

The medical analysis is primarily based on systematic reviews concerning benefits and risks of hormone contraceptives.

Besides contraceptive effectiveness, the most prevalent and worst side-effects (thromboses and neoplasies) were primarily considered as clinically relevant endpoints.

The information synthesis was done qualitatively. In conclusion, the results of information synthesis for each parameter were attributed to the following evidence levels according to the recommendations of the Oxford Centre for Evidence-Based Medicine: evidence from systematic review of randomised controlled trials (1a), clinical controlled studies (2a), case-control-studies (3a) and from non-systematic reviews (4).

Results

Effectiveness

In perfect use, hormonal contraceptives (except emergency contraceptives) proved to be the most effective reversible contraceptive methods (rate of unintended pregnancies 0.05 % to 0.3 %). Typical use of hormonal contraceptives in the form of pills, injections, patches, and vaginal rings showed a lower effectiveness (rate of unintended pregnancies 3 % to 8 %). However, this contraceptive effect was greater than the effects of all reversible hormonal contraceptives with the exception of copper spirals (evidence level 4).

Thrombotic effects

The risk of venous thromboembolism increased three to six times in users of hormonal contraceptives in comparison with non-users and declined within three months of discontinuation of applications. Users of hormonal contraceptives with inherent mutations (especially with factor V-Leiden) had a considerably higher risk of venous thromboembolism. The risk of venous thromboembolism increased with higher estrogen dose. Progestogen-only contraceptives did not demonstrate a significant effect on venous thromboembolism in any study. Contraceptives of the third generation showed a higher risk in comparison with compounds of the second generation (evidence level 2a).

The risks of stroke and myocardial infarction increased two to three times in users of hormonal contraceptives in comparison with non-users and declined after discontinuation of use. This effect was also estrogen-dose dependent. The risk of stroke increased in the contraceptives with progestogens of the first, second and third generations, the risk of myocardial infarction in the applications with progestogens of the first and second generations (evidence level 2a).

Neoplastic effects

For ovarian and endometrial carcinomas, a 0.5 and 0.7 risk reduction was shown by the use of hormonal contraceptives. This benefit increased with longer use of applications and persists 15 to 20 years after medication discontinuation (evidence level 2a).

Results for breast and cervical cancer showed an approximately 1.2 and 1.6-fold risk increase. The risk of breast cancer was higher in younger women and the risk of cervical cancer with longer duration of the medication use (evidence level 2a). The increased risk persisted several years after discontinuation (evidence level 2a).

The association between exposure to hormonal contraceptives and the risk of hepatocellular carcinoma as well as of colorectal carcinomas was inconsistent in the studies. It suggested a carcinogenic effect of hormonal contraceptives on hepatocellular carcinoma (evidence level 2a).

Other effects of hormonal contraceptives

In patients with acne, a reduction of the number of lesions as well as their severity, was proven (evidence level 1a).

The studies' results concerning sexually transmitted diseases were heterogeneous for most infections and yielded evidence only for an increase of cervical chlamydial infection (evidence level 2a). Headache, if it appeared, came mainly at the beginning of the use of combined oral contraceptives (evidence level 2a). Progestogen-only contraceptives deteriorated the results of the glucose tolerance test (evidence level 2a).

A publication of low evidence reported further risks of hormonal contraceptives concerning menstrual problems, ovarian cysts, low bone density, thyroid diseases, rheumatoid arthritis as well as further benefits with regard to blood pressure and Crohn's disease (evidence level 4).

Comparison of various hormonal with non-hormonal contraceptives

In the direct comparison of spirals with and without release of hormones, an additional contraceptive effect of hormones was proven (evidence level 1a).

Comparison of various hormonal contraceptives among each other

In emergency contraception, levonorgestrel is more effective in comparison with the Yuzpe method (estrogen-progestogen combination, two times within twelve hours, evidence level 1a). Most other proven effects (except of thrombotic effects, see above) were related to menstrual problems.

Discussion

For the most endpoints evaluated, the addressed question could be answered only on a relatively low evidence level. In many publications, studies with different estrogen doses and progestogen types were summarised. Therefore, for many endpoints it is unclear whether the currently-used contraceptives in Germany with low estrogen dose and different progestogen types have the same effectiveness.

Economic evaluation

Methods

The literature was searched in April 2006, beginning from 2000 in the most important electronic databases (MEDLINE, MEDLINE Alert, EMBASE, EMBASE Alert, SciSearch, BIOSIS, DAHTA-database, Cochrane Database of Systematic Reviews etc.). Further systematic reviews were identified through searches in publication's reference lists.

The studies' design, medical and economic assumptions as well as model assumptions, were evaluated in the presented analysis. Additionally, the transferability of the results to the current situation in Germany was checked.

Results

Two relevant health-economics studies could be included in the analysis. In typical use, Levonorgestrel and copper spirals were shown to be the most cost-effective reversible methods of contraception. Hormonal contraceptives without spirals were the next cost-effective reversible methods of contraception; the depot-medroxyprogesteron-acetate injections showed better cost-effectiveness than other appliances. Non-hormone-based methods without spirals were less cost-effective. Each method of contraception was shown to be more cost-effective than no use of contraception.

Discussion

Both studies showed some shortcomings: clinical assumptions were derived from out-dated information sources of low evidence levels and cost assumptions from the American health system for the year 2001 or 2002. Therefore, the transferability of the results to the current situation in Germany is limited.

Ethical / social and legal aspects

Methods

The literature was searched in the most important medical electronic databases. Publications for the ethical-social and legal analysis could be included only if they were primarily concerned with ethical, social or legal aspects in the use of hormonal contraceptives for healthy women of reproductive age.

Results

The literature search was conducted in April 2006 beginning from 2000 and yielded 173 hits. However, no relevant publications could be included in the analysis. Information about these aspects was used from the German Federal Centre for Health Education.

Discussion

According to the existing information about ethical and social aspects, the use of modern hormonal contraceptives seems to be relatively unproblematic. No proposal may be derived from the presented report concerning possible changes to the law.

Summary discussion of all results

For the most endpoints evaluated, the addressed questions could be answered only on a relatively low evidence level. In many publications, studies with different estrogen doses and progestogen types were summarised. Therefore, for many endpoints it is unclear whether the currently-used contraceptives in Germany with low estrogen dose and various progestogen types have the same effectiveness. The transferability of the results of the analysed primary health-economics studies on the current situation in Germany is only limited (clinical assumptions from out-dated information sources of low-evidence levels, cost assumptions from the American health system). The efficacy assumptions reflect only the typical use of contraceptives.

Conclusions

In perfect use, hormonal contraceptives (except emergency contraceptives) must be classified as the most effective reversible methods of the prevention of unintended pregnancies. For a better efficacy of hormonal contraceptives in the form of pills, injections, patches and vaginal rings under everyday conditions, interventions to improve the quality of use should be applied. Alternative methods, such as spirals with or without hormone release or hormone implants, should be prioritised if perfect use seems to be impossible.

For the individual decision concerning the use of hormonal contraceptives an individual patient's risk of thrombotic events (thromboembolism, stroke, myocardial infarction) should be estimated. Women with inherited mutations (especially with factor V-Leiden) should not use these applications.

The benefit of avoided ovarian and endometrial cancer should be related to additional risks of breast, cervical and hepatocellular carcinoma.

In women with acne, an improvement through the use of hormonal contraceptives may be expected. Cervix chlamydial infections appear to be more

frequent in users than in non-users of hormonal contraceptives.

Hormonal contraceptives may cause further benefit with regard to menstrual problems, ovarian cysts, low bone density, thyroid diseases und rheumatoid arthritis as well as further risks with regard to blood pressure and Crohn's disease.

The best application for all women cannot be derived from the presented report. Most differences between applications were related to menstrual problems.

The decision should be met individually by physicians and women. In general, combined preparations with low estrogen-dose and progestogen-only applications should be preferred. In emergency contraception, the use of levonorgestrel should be prioritised.

From a health-economics perspective in typical use the application of contraceptives on the basis of spirals is to be preferred, corresponding data in perfect use are still missing. No ethical-social or legal conclusions can be derived from the available data.

For a quantitative benefit-risk assessment of currently-used applications, the analysis of primary studies with an exclusive view on these applications is recommended. For an estimate of the incremental cost-effectiveness, a detailed health economic modelling with application of the current prices and costs in Germany would be required.

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