

newsletter

Hormonal contraceptives

Experts are currently debating the risk-benefit ratio of a range of new hormonal contraceptives in response to a growing number of reports of (sometimes) serious side effects.

Hormonal contraceptives

Hormonal formulations designed to prevent conception (contraceptives or “the pill”) contain synthetic sex hormones, which operate in a similar way to the oestrogens and gestagens produced naturally in the body. Doctors either prescribe combined oral contraceptives containing both hormones, or formulations containing only a gestagen. It is also possible to implant systems that release hormones into the body over a longer period of time. The two basic effects of such contraceptives are 1. to inhibit ovulation; 2. to inhibit the build-up of the mucous membrane within the uterus, thereby also preventing the egg from embedding itself.

Current focus

Since November 2000, Jenapharm and Schering have been offering new hormonal contraceptives under the trademarks Petibelle® and Yasmin® containing the gestagen drospirenone. Since then, there have been forty reports of deep vein thrombosis (including two deaths) linked to ethinyl estradiol and drospirenone combinations. Detailed documentation on several thrombosis cases has recently been published (BMJ, 326, 2003, 257), including a report on a 17-year-old girl – with no other known risk factors – who died of a pulmonary embolism after having taken Yasmin® for six months.

Gestagens and “generations”

Contraceptives are usually divided into various “generations”, depending on when they were brought onto the market. First-generation contraceptives include norethisterone acetate, and lynestrenol; second-generation include levonorgestrel; and third-generation include desogestrel, etonogestrel and gestodene. Dienogest and drospirenone are new developments and are not allocated to any of these “generations”.

Side effects, thromboembolisms second/third generation

Taking sex hormones such as the pill alters the hormonal balance of a woman’s body. So, in addition to preventing pregnancy, such contraceptives may cause a range of unwanted side effects. Equally, some of the side effects are considered to be desirable and have led to the authorisation of sex hormones for new indications such as the treatment of acne, hair loss, excessive, male-type body hair in women, menstrual complaints and ovarian cysts. Unwanted side effects include migrainous headaches, tension in the breasts, temporary weight gain and breakthrough bleeding.

Other serious – albeit rare – side effects include deep vein thromboses, heart attacks and strokes. It is now generally accepted that third-generation pills carry a higher risk of thrombosis than second-generation pills. On average 5-10 spontaneous cases of deep vein thrombosis will occur per 100,000 women. This rate increases to 20 cases in 100,000 women taking second-generation pills and 30-40 in the case of third-generation pills. In other words, the risk quadruples.

Pulmonary embolisms (thromboembolisms) will occur in approximately 10% of thrombosis cases, and of these 1% will turn out to be fatal. So, statistically, if one million women take a second-generation pill for a period of one year, 3 would die from fatal embolisms; in those taking third-generation pills, there would be 4.5 – 6 deaths, and in those taking third-generation pills for the first time, this figure could even be as high as nine (BMJ 323, 2001, 1). Overall, the risk associated with taking third-generation pills is therefore 50-70% higher than that associated with their second-generation equivalents.

There are still no comparative data available on the thromboembolism risk of contraceptives containing drospirenone (eg Yasmin®). However, experts are increasingly emphasising that we do not yet know enough about the risks associated with these new types of contraceptives. Reports to date – including reports of some deaths – nevertheless indicate that we are dealing with a higher degree of risk.

Risk of cancer

Medical experts are still debating a possible correlation between oral contraceptives and the occurrence of cancer. The latest report by the National Toxicology Program (Report on Carcinogens, Tenth Edition, USA), which is still purely for informational purposes and is not legally binding, included “steroidal oestrogens” in its list of potentially carcinogenic substances. Studies have led medical science to speculate that oestrogens may increase the risk of breast cancer but simultaneously reduce the risk of ovarian or uterine cancer. It is important to note that hormonal contraceptives should be clearly distinguished from formulations used in hormone replacement therapy (HRT) (see also *newsletter* 4/2002).

Plastic devices with hormone reservoir, uterine perforation

The launch of Mirena® (levonorgestrel), Nuvaring® (ethinyl estradiol/ etonogestrel) and Implanon® (etonogestrel) ushered in a range of new methods of application for hormonal contraceptives. These products are plastic devices containing a hormone reservoir which are either placed directly into the uterus like Mirena® (IUD= intrauterine device/coil) or are implanted under the skin like Implanon®. The hormone is released at a constant rate from the reservoir over a long period of time. These systems have been criticised following reports of some severe side effects such as the rupture or perforation of the coil through the uterus lining (300 reported cases following implantation of Mirena®).

In the case of Nuvaring®, the principal factors to bear in mind are the increased risk of an unwanted pregnancy (Nuvaring® can disappear unnoticed) and the higher incidence of vaginal inflammation. Extensive abnormal bleeding as well as severe pain and acne are among the symptoms that have been observed in women taking Implanon®.

Conclusion

From a risk management perspective, the entire group of hormonal contraceptives represent a significant exposure. Thromboembolisms are a rare but serious side effect of combined hormone pills. It is generally accepted that third-generation contraceptives carry 50-70% more risk than their second-generation counterparts. The risk of thrombosis associated with contraceptives containing drospirenone cannot yet be definitively assessed as more research still has to be carried out on the subject. However, the growing number of reported (sometimes fatal) thromboses would suggest that these products also involve significant risks. In response to these reports, doctors in Holland have been instructed by medical authorities not to prescribe these formulations. Likewise, new types of contraceptive such as the intrauterine device (IUD) Mirena® and the vaginal ring Nuvaring® have been criticised on account of their negative risk-benefit ratio compared to traditional hormonal contraception methods. Many medical experts point out that too little is known about the long-term impact of these formulations.

Information for the underwriter

Formulations containing third-generation hormones do not demonstrate significant added value compared to second-generation equivalents and involve a much higher risk of thrombosis. This may expose insurers to product liability claims, and there is even a possibility that products may be withdrawn from the market altogether. Diane® is an example of a contraceptive that was withdrawn from the market in 1994 and then relaunched following approval for a new indication for use as an acne treatment.

The risk-benefit ratio of implantable systems should be scrutinised very carefully, as these products may also be withdrawn from the market in the future. Equally, contraceptives containing drospirenone may lead to liability claims. The future risk-benefit ratio of these products remains to be seen. However, any doctor prescribing them may be held liable if he/she fails to explain the risks, side effects and alternatives to a patient adequately. It is currently standard medical procedure to advise women on a Mirena® implant as an alternative to ligature of the fallopian tubes. We may therefore expect the number of users to rise, and, consequently, the number of reports of severe side effects to increase in tandem.

We cannot be certain that medical science will not establish a direct correlation between the use of synthetic sex hormones as contraceptives and cancer at some point in the future. So we should also reckon with possible market withdrawals in this area. In Britain a class action case has already been filed. Even though this particular case has been dismissed, it does not preclude the possibility of courts in other countries (notably US/Canada) coming to different verdicts.

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