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Review article

Medical eligibility criteria for new contraceptive methods: combined hormonal patch, combined hormonal vaginal ring and the etonogestrel implant

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Abstract

To review evidence on the combined hormonal patch, combined hormonal vaginal ring and the etonogestrel implant, with a focus on safety and effectiveness of use among women with special health conditions, we searched MEDLINE, Pre-MEDLINE and the Cochrane Library for reports published from 1980 through March 2005. Articles eligible for review included 11 on the hormonal patch, nine on the hormonal ring, and 11 on the etonogestrel implant. Limited evidence suggests patch efficacy is lower among women >90 kg. No evidence was identified for vaginal ring use among women with medical conditions. A single small study found that etonogestrel implants had no adverse effects on bone mineral density among women 18–40 years old. Limited evidence also suggests no adverse effects of the etonogestrel implant on lactation parameters or infant development among users enrolled 28 to 56 days postpartum and followed for 4 months.

Keywords: Evidence-based guidelines; Combined hormonal patch; Combined hormonal vaginal ring; Etonogestrel implant

1. Introduction

Every year, approximately 210 million women become pregnant and as many as 80 million of these pregnancies are unplanned [1]. Since the introduction of oral contraceptives, research has focused on modifying the dosage of estrogen and progestogen formulations to improve safety and acceptability, and on identifying new contraceptive delivery systems to increase effectiveness by improving user compliance [2]. Poor adherence to pill regimens is responsible for the substantial difference between the percentage of women experiencing an unintended pregnancy within the first year of use of oral contraceptives with perfect use (0.3%) and typical use (8%) [3].

Development of a combined hormonal transdermal contraceptive patch was initiated in the early 1990s, and the first patch was approved by the US Food and Drug Administration in early 2002 under the names Ortho Evra™/Evra™ [4]. The contraceptive patch is a 20-cm^2 system composed of three layers: an outer protective polyester layer, a medicated adhesive middle layer and a release liner that is removed prior to patch application. The patch has been designed to mimic the 28-day dosing schedule of combined oral contraceptives (COCs): during the 21 days of active hormone delivery, the patch releases 150 μg of norelgestromin (NGMN) and 20 μg of ethinyl estradiol (EE) daily to the systemic circulation; afterwards, there is a 7-day patch-free (i.e., hormone-free) period. Application sites for the patch include the buttocks, upper outer arm, lower abdomen or upper torso [5].

The combined hormonal vaginal ring (NuvaRing®, Organon, West Orange, NJ, USA) is a newly approved contraceptive delivery system that follows a 28-day cycle similar to COCs: each cycle, the ring is worn for 21 days, followed by seven ring-free days. The vaginal ring is a lightweight ring made of ethylene vinyl acetate (EVA) copolymer that continuously releases 120 μg of etonogestrel and 15 μg of EE daily [6]. At the end of every 28-day cycle, a new vaginal ring is inserted into the vagina.

In 1998, an etonogestrel implant (Implanon®) developed by NV Organon (Oss, The Netherlands) was introduced in Indonesia [7]. This implant is a single rod releasing the desogestrel metabolite, etonogestrel (3-keto-desogestrel),

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which is approved for up to 3 years of use [8]. The implant is made of EVA, is 40 mm in length and 2 mm in diameter, and contains a core of 68 mg of etonogestrel [9]. At insertion, approximately 60–70 μg/day of etonogestrel is released, with the rate falling steadily to about 25–30 μg/day by the end of the third year [10]. Studies indicate that ovulation suppression accounts for nearly all of the contraceptive effect of the etonogestrel implant over the 3 years [11]. In addition, impaired cervical mucus and poor sperm penetration may contribute to the contraceptive efficacy, and suppression of endometrial development has been shown as well [11]. After discontinuation, serum concentrations of etonogestrel fall to undetectable levels within 1 week [10], and ovulation occurs within 6 weeks [12].

We conducted systematic reviews of published evidence on the safety of the commercially available contraceptive patch (Ortho Evra™/Evra™), vaginal ring (NuvaRing®) and etonogestrel implant (Implanon®) for women of reproductive age according to the 77 medical conditions identified by the World Health Organization (WHO) for eligibility for contraceptive use [13]. In this report, we describe the evidence obtained through these reviews, which was prepared for an Expert Working Group of international family planning experts convened by WHO in October 2003, to develop and revise medical eligibility criteria for contraceptive use. This review also includes evidence identified since the 2003 meeting through March 2005.

2. Materials and methods

We searched MEDLINE, Pre-MEDLINE and the Cochrane Library for reports published in English from 1980 through March 2005 relating to the use of the combined hormonal patch, combined hormonal vaginal ring or etonogestrel implant among premenopausal women of reproductive age for 77 conditions included in WHO medical eligibility criteria guidelines. In addition, we included published reports from pharmacokinetic studies to supplement evidence from clinical studies. The following terms were used to retrieve reports from MEDLINE and Pre-MEDLINE: "contraceptive agents, female" AND "patch"; "contraceptive agents, female" AND "ring" AND "vagina"; and "Implanon OR (etonogestrel and implants)". Search terms to identify Cochrane reviews included the following: "contracept* AND patch", "contracept* AND ("vagina" OR "ring"); and "contracept*" AND "implant". We handsearched reference lists from articles identified through bibliographic database searches to include additional articles relevant for the reviews.

The search strategy identified a total of 316 articles and one Cochrane review for the three contraceptive methods. Articles that examined the safety or effectiveness of these methods among women with a specific health characteristic or condition were considered as direct evidence for this systematic review. Since we identified very little direct evidence, we included articles among healthy women that examined safety or effectiveness of use of these contraceptive methods as indirect evidence. We excluded articles without original data, review articles, studies of postmenopausal women, studies of hormonal rings with hormone formulations different than NuvaRing® and studies of implants releasing progestogens other than etonogestrel.

Eleven articles on the patch and nine on the vaginal ring were eligible for review. We did not include the Cochrane review because the two randomized controlled trials (RCTs) on the patch were already retrieved by our search, and no RCT on the vaginal ring was identified. Eleven articles on the etonogestrel implant were eligible for the review.

Evidence from each study was summarized on a standard abstract form [14], indicating the study design, study population, main exposures and outcomes, and potential threats to internal validity (i.e., selection bias, reporting bias, misclassification, loss to follow-up, etc.). The quality of the evidence presented in each individual study was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) System, which assigns a rating of very low, low, intermediate or high according to the strength of the study design and the interval validity of the study [15]. We summarized ratings across individual studies to reflect the quality of the body of evidence for each new contraceptive method. We were unable to compute summary measures of association (i.e., Peto odds ratios) due to the heterogeneity among study populations and dissimilar study designs.

3. Results

3.1. Combined hormonal patch

Direct evidence regarding use of the combined hormonal patch among women with health conditions was available for two conditions—age and obesity (Table 1). Due to the lack of evidence for women with other medical conditions, we reviewed evidence among healthy women as indirect evidence.

3.1.1. Age

No serious adverse events were reported by two small, noncomparative studies of healthy adolescents using the patch [16,17]. Thirty-one percent of users complained of breast discomfort and less than 15% experienced headaches, spotting, cramping or bleeding between menses.

3.1.2. Obese women

Limited evidence from two studies found that heavier women may have a greater risk of contraceptive patch failure. A North American trial reported five pregnancies among patch users, of which four were attributed to patch failure [18]. Body weight among the women who experienced a patch failure ranged from 48.2 to 93.2 kg (median=74.5 kg). Similarly, a prospective study found that the incidence of pregnancy among contraceptive patch