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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

Table 1
Evidence on the combined hormonal patch

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Rubenstein et al., 2004 [16]	Noncomparative study	50 women	Compliance, adverse effects	Follow-up: 80% at 1 month, 62% at 3 months; compliance: 87% of girls in study at 3 months	Very low
	3 months	15–18 years		No pregnancies	
	USA	<90 kg		Adverse effects: 31% had breast discomfort, <15% reported more headaches, spotting, cramping, bleeding between menses	
Logsdon et al., 2004 [17]	Noncomparative study	62 women	Compliance, adverse events	17.6% discontinued using patch—Reasons for discontinuation: 5% skin irritation, 5% patch detachment, 6.7% economics	Very low
	10 cycles	Mean=17.9 years		No pregnancies	
	USA				
Pierson et al., 2003 [22]	Randomized open-label trial	124 women	Follicular size, ovulation defined by disappearance of follicle, side-effects	Follicle size significantly smaller for patch vs. COC group during normal cycle and cycle with dosing error. Occurrence of ovulation significantly less in patch group	Intermediate
	5 cycles (dosing error in Cycle 4): 1) 10 days patch or 7 days patch+3 days patch-free	52 patch, 72 COC			
	USA and Canada	18–35 years			
Dittrich et al., 2002 [21]	Randomized study	610 women	Compliance, ovulation activity, adverse events	Compliance: 94.7% (P) vs. 78% (COC)	Low
	4 cycles	3 patch size groups: 10, 15, 20 cm^2 (n=450) vs. 150 COC		20-cm^2 patch (P) vs. COC: 6.2% (P) vs. 7.2% (COC) ovulated; 5.4% (P) vs. 4.3% (COC) luteal activity; 88.4% anovulation P and COC; 6.7% (P) skin reaction	
	Europe, USA, South Africa	18–45 years			
Audet et al., 2001 [18]	Randomized, open-label trial	1417 women	Pearl indices, adverse events	Pearl index (patch vs. COC): 1.24 (0.15–2.33) vs. 2.18 (0.57–3.80) overall, 0.99 (0.02–1.96) v. 1.25 (0.02–2.47) due to method failure	Intermediate
	6 and 13 cycles	812 patch vs. 605 COC		4 pregnancies in users weighing 80, 93.2, 74.5, 48 kg	
	USA and Canada	18–45 years		Adverse events: migraine, cholecystitis, paresthesia in arm. Complaints (patch vs. COC): 18.7% vs. 5.8% breast dis comfort, 13.3% vs. 9.6% dysmenorrhoea, 20.2% vs. 0% application site reaction	
Smallwood et al., 2001 [19]	Noncomparative open-label study	1171 (6 cycles) and 501 (13 cycles)	Pearl index, adverse events	Pearl cycle 1–6: 0.4% (overall and due to method failure); Cycles 7–13: 0.7 (overall), 0.4 (method failure)	Low
	6 and 13 cycles			Weights (kg) of women who experienced method failure: 93.2, 89.5, 90, 61.8, 95 kg	
	Europe, Israel, Australia, USA			Adverse events: cervix adenocarcinoma in situ, menorrhagia, pulmonary embolism (protocol violation)	

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Table 1 (*continued*)

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Helmerhorst et al., 2000 [20]	Randomized, open-label trial for 6 and 13 cycles Europe and South Africa	1517 women 861 patch, 656 COC 18–45 years	Pearl indices, adverse events	Pearl index (patch vs. COC): 0.88 v. 0.56 Complaints (% patch vs. % COC): breast discomfort (25% vs. 9.5%), headaches (20% vs. 24%), application site reaction (14% vs. 0), nausea (12% vs. 6%), abdominal pain (11% each), dysmenorrhoea (5% each)	Low

users increased with increasing body weight [19]. Six pregnancies occurred during patch use from which five were attributed to method failure, and four of these five women weighed 90 kg or more.

3.1.3. Indirect evidence

Two studies (one randomized [18], one noncomparative [19]) reported a total of six serious adverse events attributed to patch use among healthy women—migraine, cholecystitis, paresthesia in the arm of patch application, adenocarcinoma in situ of the cervix, menorrhagia and pulmonary embolism (Table 1). The pulmonary embolism was attributed to a protocol violation and resolved with therapy. Compared with women using COCs, patch users were significantly ($p<.05$) more likely to experience skin site reactions [18,20–22], breast discomfort [18,20], dysmenorrhea [18] and nausea [18–21]. Elevations in mean total cholesterol and triglyceride levels were observed in patch users compared with COC users; however, the changes were not considered clinically meaningful [18,21].

3.1.4. Pharmacokinetic evidence

In addition to the epidemiologic evidence, we examined pharmacokinetic studies comparing the patch with COCs. Three randomized studies investigated the pharmacokinetics of patch hormones under various conditions in healthy women [23–25]. For these studies, reference ranges for NGMN and EE were developed according to calculated average serum concentrations in 90% of individual subjects taking an oral equivalent of NGMN and EE over a 24-h period, to identify efficacious concentrations of NGMN and EE released by the patch [24]. In general, regardless of patch application site [23], dermal exposure to heat, humidity, or exercise [24], or duration of patch wear [25], NGMN and EE levels remained within the reference range.

3.2. Combined hormonal vaginal ring

Evidence directly applicable to the health effects of vaginal ring use among women with medical conditions was not available. Therefore we reviewed evidence from five studies among healthy women as indirect evidence (Table 2).

3.2.1. Indirect evidence

Across five studies, three serious adverse events were reported: two cases of deep vein thrombosis (DVT) and one case of strabismus [26,27]. The DVT cases were believed to be related to ring use. The most frequent complaints of ring users included headaches (5.8%) and vaginitis (5.6%); fewer than 5% of users experienced leukorrhea, device-related events, weight increase, nausea, emotional lability, breast tenderness, dysmenorrhea, vaginal discomfort, changes in Papanicolaou (Pap) smear grade and acne [26,28]. Ring users participating in one randomized trial [27] were more likely to experience leukorrhoea (3.5% vs. 0.2%) and vaginitis (3.9% vs. 1.0%) compared with COC users; in another randomized trial [28], more ring users complained of vaginitis (4.1% vs. 1.6%) and decreased libido (8.3% vs. 0) than COC users. According to a noncomparative study, cervical cytology was normal for 98% of women (2271/2322) from baseline through 13 cycles. For 33 women, cervical cytology was normal at baseline and shifted to a low-grade squamous intraepithelial lesion during the study. Another seven women experienced a shift from normal baseline cytology to abnormal, high-grade squamous intraepithelial lesion–carcinoma in situ at the last assessment. Eleven women were diagnosed with a low-grade squamous intraepithelial lesion at baseline and Pap smear results returned to normal for eight of them after 13 cycles and did not worsen for the remaining three women [26]. Studies investigating the cervicovaginal epithelium and vaginal flora pre- and post-ring use did not detect meaningful changes in columnar or squamous epithelium [6], the vaginal flora [29], or presence of human papilloma virus (HPV) [6]. A case of mild vaginal dysplasia was diagnosed in one ring user who had polyclonal aneuploidy prior to participating in the study [6]. Finally, in comparative studies [27,30–32], no observed clinically relevant differences in blood pressure, blood chemistries, heart rate, adrenal and thyroid function, carbohydrate metabolism or hematology

Table 2
Evidence on the combined hormonal vaginal ring

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Oddsson et al., 2005 [27]	Randomized open-label trial 13 cycles 9 European countries, Brazil and Chile	1030 healthy women ≥18 years 512 NuvaRing, 518 COC	Adverse events, tolerance, contraceptive efficacy	Pregnancies: 10 total=ring: 5, COC: 5. 5/10 were protocol violations Pearl indices: ring=1.23 (95% CI 0.40–2.86), COC=1.19 (0.39–2.79) Serious events: deep vein thrombosis (ring), hypertension (COC) Adverse events: 28.9% ring, 22.1% COC due to method (confirmed by author); vaginitis (3.9%) and leukorrhoea (3.5%) reported more by ring users	Intermediate
Magnusdottir et al., 2004 [31]	Nonrandomized study 6 cycles Iceland	87 healthy women 18–40 years 44 NuvaRing, 43 COC	Hemostatic variables: coagulation and fibrinolysis markers; adverse events	Procoagulation variables: factor VII activity higher ($p<.001$) at Cycle 6 for ring vs. COC users; post-treatment levels not significantly different Anticoagulation variables: higher protein C levels for ring vs. COC at Cycle 3 ($p<.001$), at Cycle 6 (NS) and post-treatment (NS); higher antithrombin III for ring vs. COC; protein S higher for ring at Cycle 3 but lower than COC at Cycle 6 and post-treatment Profibrinolysis variables: plasminogen activity increased for both (Cycles 3 and 6), activator t-PA lower for ring vs. COC; plasmin–antiplasmin (PAP) complexes elevated at Cycles 3 and 6 for both; plasminogen, PAP complexes and t-PA returned to baseline levels for ring and COC post-treatment Antifibrinolysis: no significant differences between ring and COCs Fibrin turnover: no significant differences between ring and COCs. No serious adverse events reported	Low
Tuppurainen et al., 2004 [30]	Nonrandomized study 6 cycles Finland	83 healthy women 18–40 years 40 NuvaRing, 43 COC	Lipid profile, sex hormone binding globulin (SHBG), corticosteroid binding globulin (CBG), adverse events	Total cholesterol unchanged with ring HDL-cholesterol significantly higher for ring cycles 3 and 6 vs. COC ($p<.01$), HDL (2) increased with ring, HDL (3) decreased with ring LDL-cholesterol lower at cycle 3 and 6 for ring vs. COC Triglycerides increased for both methods SHBG increased for both methods, levels higher for ring ($p<.01$) CBG increased for both, levels lower for ring vs. COC ($p<.01$) Adverse events: strabismus and deep vein thrombosis (ring), depression (COC)	Low
Bjarnadottir et al., 2002 [28]	3 trials: 1 randomized, 2 non-randomized 6 cycles Europe	247 healthy women 18–40 years 121 NuvaRing, 126 COC	Adverse events, cycle control	Adverse events: 33.9% ring and 24.6% COC had a minor adverse event; in the ring group, <5% each for acne, breast discomfort, device-related discomfort, headache, nausea, leukorrhoea, vaginitis, vaginal discomfort, weight increase, nervousness; 8.3% lower libido	Low

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Table 2 (*continued*)

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Dieben et al., 2002 [26]	Pooled, 2 noncomparative studies 13 cycles Europe, USA, Canada	2322 healthy women 18–40 years	Pregnancy rate, adverse events, cycle control	Pregnancies: 21 Pearl indices: 1.18 (95% CI 0.68–1.69) overall, 0.77 (95% CI 0.34–1.4) per protocol; pregnancy rate=1.18% Adverse events: 5–6% headaches, vaginitis, bleeding/spotting; <5% had leukorrhoea, weight increase, device-related discomfort; <4% nausea, emotional lability, breast tenderness, acne, dysmenorrhoea, vaginal discomfort	Low
Roumen et al., 1996 [6]	Prospective, noncomparative study 20 cycles Netherlands	76 healthy women 18–35 years	Cytological changes in cervix and vagina, bacterial flora, HPV status, morphology of cervix	No cytology changes, HPV detected in 3 subjects with reversion to negative in 2, aneupoloidy in 11 subjects with 7 changing to diploid, could not establish significance on vaginal flora, 1 case of mild dysplasia diagnosed	Very low
Davies et al., 1992 [29]	Prospective, noncomparative study 1 cycle for varying periods of time UK	59 healthy women Ring use groups: 15=21 days, 15=28 days, 14=42 days, 15=56 days	Vaginal flora (*Gardnerella vaginalis*, streptococci, yeast), gonorrhea, chlamydia	No significant changes in pre- or post- ring vaginal flora, bacteria or inflammatory cells	Low

were observed as a result of ring use compared with women using COCs.

3.2.2. Pharmacokinetic evidence

The pharmacokinetics of the vaginal ring were compared with those of a COC [150 μg desogestrel, 30 μg EE] in a randomized, crossover trial [33]. Although maximum serum concentrations were lower and the time to reach peak concentrations was longer with the ring, the absolute bioavailability of hormones from the ring was either higher (progestins) or similar (estrogens) to hormones delivered by COCs. No difference in progestin half-lives was observed between the two groups; however, the half-life of estrogen with the ring extended 15 h beyond that measured with the COC.

3.3. Etonogestrel implant

Evidence from studies directly relevant to three medical conditions—age, breastfeeding and endometriosis—was available for the etonogestrel implant (Table 3). Due to the lack of evidence for other medical conditions, we reviewed evidence among healthy women as indirect evidence for this implant.

3.3.1. Age and the effects of etonogestrel implants on bone mineral density

In a small study investigating bone mineral density (BMD) among 73 women, 18–40 years of age, using the etonogestrel implant or a hormone-free IUD, increases in BMD were recorded at the lumbar spine, femur and radius, but not at the femoral neck over 2 years [34]. Regardless of anatomical site or age and weight at baseline, BMD did not significantly differ between etonogestrel implant and IUD users, and estrogen levels among etonogestrel implant users were not correlated with BMD. We did not identify any studies of etonogestrel implant use and effects on BMD for the age groups of greater concern — those less than age 18 and greater than age 45.

3.3.2. Breastfeeding

According to a study of breastfeeding women who were enrolled 28 to 56 days postpartum, use of the etonogestrel implant did not significantly affect parameters of breastfeeding (milk volume, content, production) or infant growth or development compared with nonhormonal IUD users over a 4-month period [35].

3.3.3. Endometriosis

In a case series of five women with severe pelvic endometriosis, etonogestrel implant treatment offered relief from painful symptoms in all five women over the period of etonogestrel implant use, which varied from 3 months to 3 years [36]. No adverse events occurred.

3.3.4. Indirect evidence

In prospective studies where healthy women were randomly assigned to use etonogestrel or levonorgestrel (LNG) implants, no significant differences between

Table 3
Evidence on the etonogestrel implant

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Yisa et al., 2005 [36]	Case series 3 years UK	5 women 35–45 years	Treatment of symptoms due to severe endometriosis	Implant relieved pain in 5 women and no adverse events reported	Very low
Biswas et al., 2004 [40]	Randomized, comparative study 2 years Singapore	80 healthy women 29.1±4.6 years 40 etonogestrel, 40 LNG implant	Liver function tests [total and unconjugated bilirubin, albumin, liver enzymes—alanine transferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and lactate dehydrogenase (LDH)]	Conjugated bilirubin: 7-fold increase for both methods at 2 years, but levels within normal population range AST and LDH levels higher for Implanon at year 1 ($p<.01$) GGT levels increased for both implants from baseline Serum albumin: no significant changes for either method	Intermediate
Smith and Reuter, 2002 [42]	Retrospective chart review and mailed survey 1 year UK	190 women 13–51 years	Continuation rates, adverse events	88% continued etonogestrel implant use for 6 months, 78% for 12 months; no pregnancies Among removals: 34% bleeding problems, 24% mood swings, 17% headache, 12% weight gain, 10% desired pregnancy	Low
Biswas et al., 2001 [38]	Randomized comparative study 2 years Singapore	80 women 18–40 years 40 etonogestrel, 40, LNG implant	Oral glucose tolerance test, plasma glucose and insulin levels	At 24 months, 2-h response to glucose was 10% higher than baseline for etonogestrel implant ($p<.05$); 2-h response for insulin increased 70% from baseline for etonogestrel implant ($p<.05$). Fasting levels of glucose and insulin, and levels of HbAC consistent over time, except for significant increase in fasting levels of insulin at 24 months. Values were within WHO criteria for impaired glucose tolerance	Intermediate
Beerthuizen et al., 2000 [34]	Comparative study 2 years Chile and Europe	73 women 18–40 years 44 etonogestrel, 29 nonhormonal IUD	Bone mineral density at lumbar spine, femur, distal radius	Mean decrease of 1 SD not reached at any point; BMD increases slightly greater for etonogestrel implant vs. IUD; no site differences in BMD, slight decrease at femoral neck; estrogen level not associated with BMD change	Low
Biswas et al., 2000 [37]	Randomized comparative study 2 years Singapore	80 women 18–40 years 40 etonogestrel, 40 LNG implant	Fasting blood levels for total thyroxin, TBG, CBG, testosterone, SHBG, albumin	Thyroid T3 and T4 changed little from baseline thru the 24 months. TBG declined at 6 and 12 months, and increased at 24 months. Declines in total testosterone observed for both implants; SHBG declined at 6 and 12 months, and increased at 24 months for etonogestrel; SHBG decreased at all times for LNG and statistically different from Implanon. Increased cortisol levels observed for both implants. Albumin levels slightly increased for both, but less than 5%	Intermediate
Reinprayoon et al., 2000 [35]	Prospective comparative study 4 months Thailand	80 women 18–40 years 40 etonogestrel implant, 40 nonhormonal IUD	Breast milk production and content, infant development, infant etonogestrel exposure	No significant difference in milk quality or quantity for either method, slightly more milk fat in IUD breast milk; infant etonogestrel exposure was 19.86 ng/kg per day at 1 month and decreased over time; no difference in head circumference or incidence of illness	Intermediate

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Table 3 (*continued*)

Author, year, reference #	Study design	Population	Outcome measure	Results	Grading
Edwards and Moore, 1999 [41]	Meta-analysis of comparative and noncomparative studies	2791 women	Adverse events, clinical parameters	No significant differences in adverse events between etonogestrel and LNG implants	Low
	2 years Europe, South America, Indonesia	18–40 years		BP levels not significantly different: systolic increase of 0.6 (etonogestrel) and 0.7 (LNG), diastolic increase of 0.6 (etonogestrel) and 0.7 (LNG)	
Suherman et al., 1999 [39]	Prospective, semirandomized study	135 women	Blood chemistry, pregnancy, weight gain, cervical smear cytology, adverse events	No difference: triglycerides, HDL cholesterol, mean lipid profile across methods; total cholesterol and LDL tended to decrease over time with all methods. Apolipoproteins: AI trends for etonogestrel not clear; AII levels constant, and B levels slightly reduced	Intermediate
	3 years Singapore	18–40 years 45 etonogestrel and 45 LNG implant, 45 nonhormonal IUD			

implants were found with regard to thyroid hormone levels, adrenal function [37], carbohydrate metabolism [38], lipid metabolism [39] or liver function [40]. Similarly, a meta-analysis of safety studies did not identify any significant differences between etonogestrel and LNG implant users with respect to side effects, serious adverse events or impact on blood pressure measures [41]. Fewer than 10% of etonogestrel or LNG implant users experienced side effects related to skin and limbs (7.4% vs. 8.5%), the nervous system (5.2% vs. 7.4%) or psychiatric symptoms (4.3% vs. 5.2%); less than 5% of women using an etonogestrel or LNG implant reported events related to other body systems [41]. A review of medical charts noted that less than one-third of users recorded complaints due to their etonogestrel implant, and primary reasons for discontinuation included irregular bleeding (34%), mood swing (24%), headache (17%), weight gain (12%) and desire for pregnancy (10%) [42].

3.3.5. Pharmacokinetic studies

In pharmacokinetic studies of the etonogestrel implant, nearly 100% bioavailability of etonogestrel was observed over 2 years, with constant and rapid clearance of etonogestrel from the circulation [43], and an inverse relation between serum concentrations of etonogestrel and increasing body weight [43]. Mean etonogestrel concentrations were highest among women weighing <50 kg, followed by women weighing 50–60, 60–70 and >70 kg [10].

4. Discussion

Evidence on the combined hormonal patch, combined hormonal vaginal ring and etonogestrel implant was limited, and research was primarily conducted among presumably healthy women. To date, no studies have examined whether the avoidance of the first-pass effect through the liver with patch or ring use lessens concerns about drug interactions or use of these methods by women with liver conditions. In addition, epidemiological data on the long-term effects of patch, ring or etonogestrel implant were not available.

Two small studies [16,17] reported no serious adverse events resulting from patch use among adolescent users. Moreover, adolescents participating in these studies experienced side effects that were similar in type and frequency to those reported by older women in other studies [18,20]. Limited evidence from two studies that included very small samples of women weighing more than 90 kg [18,19] suggests that patch efficacy declines among women whose weight exceeds 90 kg; however, neither study presented information on safety for women >90 kg. An analysis that pooled the data from these individual studies confirmed these findings [44]. Evidence from two randomized trials among healthy women suggests that patch users experience the same side effects as users of COCs with similar hormone formulations with the exception of breast discomfort, application site reactions and dysmenorrhea. Women who had contraindications preventing them from taking steroid hormones or those with other medical conditions were excluded from the studies, but obese women were included. Further, while clinical study sample sizes were sufficiently large (N>1000 women), few safety studies offered appropriate comparison groups, most relied on self-reported data, no adjustments were made for possible confounding variables and most failed to provide enough information to assess whether selection bias was present or not. Given these limitations, the quality of the body of evidence for both age and obesity conditions received a very low grade, and the indirect body of evidence was graded as intermediate.

For the vaginal ring, we identified no direct evidence regarding women with medical conditions. Indirect evidence among healthy women suggests that the ring does not alter vaginal flora [6,28,29], and one study reported that ring use among women with low-grade squamous intraepithelial

Table 4
Medical eligibility categories for the combined hormonal patch, combined hormonal vaginal ring and etonogestrel implant among women with special conditions [13]

Condition		WHO eligibility category[a]		
		Combined hormonal patch	Combined hormonal vaginal ring	Etonogestrel implant
Breastfeeding	<6 weeks	4	4	3
	6 weeks–6 months	3	3	
Postpartum	<21 days	3	3	
Smoking ≥35 years	<15 cigarettes/day	3	3	
	≥15 cigarettes/day	4	4	
Multiple cardiovascular disease risks		3/4[b]	3/4[b]	
Hypertension	History where BP CANNOT be evaluated or adequately controlled where BP can be evaluated	3	3	
Elevated BP	Systolic 140–159 or diastolic 90–99	3	3	
	Systolic>160 or diastolic >100	4	4	
	Vascular disease	4	4	
Deep venous thrombosis/ pulmonary embolism	History of DVT/PE	4	4	
	Current DVT/PE	4	4	3
	Major surgery, with prolonged immobilization	4	4	
Known thrombogenic mutations		4	4	
Current and history of ischaemic heart disease		4	4	I=2, C=3
Stroke (history of cerebrovascular accident)		4	4	I=2, C=3
Known hyperlipidemias		2/3[b]	2/3[b]	
Valvular heart disease	Complicated	4	4	
Headaches—migraine	Without aura, <35 years	I=2, C=3	I=2, C=3	
	Without aura, ≥35 years	I=3, C=4	I=3, C=4	
	With aura at any age	4	4	
Unexplained vaginal bleeding			3	
Breast disease—cancer	Current	4	4	4
	Past and no evidence of current disease for 5 years	3	3	3
Diabetes—nephropathy/ retinopathy/neuropathy or other vascular disease or diabetes of ≥20 years' duration		3/4[c]	3/4[c]	
Gall bladder disease, *medically treated or current*		3	3	
History of cholestasis, *past COC-related*		3	3	
Viral hepatitis—active		4	4	3
Cirrhosis	Mild (compensated)	3	3	
	Severe (compensated)	4	4	3
Liver tumors — benign or malignant		4	4	3
Drug which affects liver enzymes—rifampicin or certain anticonvulsants		3	3	3

I, initiation of method; C, continuation of method.

[a] WHO Medical Eligibility Categories: 1=A condition for which there is no restriction for the use of the contraceptive method; 2=A condition where the advantages of using the method generally outweigh the theoretical or proven risks; 3=A condition where the theoretical or proven risks usually outweigh the advantages of using the method; 4=A condition which represents an unacceptable health risk if the contraceptive method is used.

[b] Category should be assessed according to the type, severity, and presence of other cardiovascular risk factors.

[c] Category should be assessed according to the severity of the condition.

lesions did not worsen this condition [26]. Evidence from two randomized trials among healthy women showed that ring users experienced similar side effects compared with COC users [27,28], and the incidence of side-effects among healthy ring users in noncomparative studies [6,26] was similar to what was reported in the randomized studies.

Several studies lacked a comparison group, did not randomize subjects, included few subjects ($N<300$) and did not adjust for confounding or adequately describe subject selection criteria to rule out selection bias; however, the randomized trials elevated the quality of the body of indirect evidence to an intermediate grade.

Evidence from one small study [35] of women using the etonogestrel implant found BMD was not adversely affected among women 18–40 years of age over 2 years. Changes in BMD among etonogestrel implant users were comparable to those observed in women using a hormone-free IUD. Despite an appropriate control group and detailed exposure and outcome assessments, this study provides evidence of low quality because treatment was not blinded, the discontinuation rate was high, the sample size was small ($N<100$) and there was no adjustment for confounding variables. According to a study of intermediate quality, lactation and infant development parameters among etonogestrel implant users were comparable to those of hormone-free IUD users over 4 months observation [34]. Limited evidence of very low quality from five women with severe endometriosis found that etonogestrel implant users did not experience any adverse effects and that the etonogestrel implant may offer relief from painful symptoms [34]. Finally, observational studies among healthy women found that users of the etonogestrel implant did not experience significantly different side-effects compared with LNG implant users [37–42]. Despite variations in the types of studies included in the body of indirect evidence, an intermediate grade was assigned owing to two randomized trials among the studies included.

To review this evidence and develop recommendations for medical eligibility criteria for these new hormonal contraceptive methods, an Expert Working Group of 36 participants from 18 countries, including representatives of many agencies and organizations, convened at WHO on 21–24 October 2003. Pending new evidence on the patch or the ring, the Working Group applied the same medical eligibility categories assigned to medical conditions for COCs to the patch and ring. Similarly, for conditions without direct evidence for the etonogestrel implant, evidence on LNG implants was applied. In general, these new contraceptive methods can be used (WHO Category 1) or can generally be used (WHO Category 2) by women with most medical conditions. Table 4 summarizes medical conditions for which women should not use (WHO Category 4) or generally should not use (WHO Category 3) the patch, vaginal ring or etonogestrel implant. The assigned categories should be considered a preliminary, best judgment, which will be reevaluated as new data become available.

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