Acta Obstetricia et Gynecologica. 2010; 89: 670–676

informa
healthcare

MAIN RESEARCH ARTICLE

A randomized clinical trial of two emergency contraceptive pill regimens in a Ugandan population

JOSAPHAT K. BYAMUGISHA[1,2], FLORENCE M. MIREMBE[1], ELISABETH FAXELID[2], NAZARIUS M. TUMWESIGYE[3] & KRISTINA GEMZELL-DANIELSSON[4]

[1]*Department of Obstetrics and Gynecology, Makerere University, Faculty of Medicine, Kampala, Uganda,* [2]*Department of Public Health Sciences, Division of International Health (IHCAR), Karolinska Institutet, Stockholm, Sweden,* [3]*Department of Epidemiology and Biostatistics, Makerere University, School of Public Health, Kampala, Uganda, and* [4]*Department of Woman and Child Health, Division of Obstetrics and Gynecology, Karolinska Institutet, Stockholm, Sweden*

Abstract

Background. Recent trials on emergency contraception (EC) have indicated that levonorgestrel (LNG) used alone has fewer side-effects and is more efficacious than the Yuzpe regimen (high dose combined oral contraceptive pills). However, the experienced side-effects and acceptability may vary between different groups or societies. *Objective.* The primary objective of this study was to determine side-effects and acceptability of two emergency contraceptive pill (ECP) regimens among users in Kampala, Uganda. *Study design.* Randomized clinical trial. *Methods.* A total of 337 women were enrolled in a double blind randomized clinical trial. Women requesting ECPs within 72 hours after unprotected sexual intercourse received either LNG or the Yuzpe regimen. The women returned for follow-up after three days and a follow-up interview was performed after one year. *Results.* Levonorgestrel had significantly fewer side-effects than the Yuzpe regimen ($p < 0.001$). There was a significant association between having worries about the method and experiencing side-effects ($p < 0.001$). Most women (81%) were prime users of EC. The majority would recommend ECP to other clients. *Conclusions.* Levonorgestrel is a superior option to the Yuzpe regimen and should be promoted as the recommended ECP. Having worries about ECP may influence experience of the side-effects. Correct information is critical in promotion of ECP use.

Key words: *Emergency contraceptive pills, levonorgestrel, Ugandan*

Introduction

The emergency contraception (EC) drug regimens currently available world wide include progestin only drug combinations such as levonorgestrel (LNG), the Yuzpe regimen and the intrauterine contraceptive copper-device (IUD) (1). The most commonly used EC method has been the Yuzpe regimen, which consists of 0.1 mg ethinyl estradiol and 0.5 mg LNG taken twice 12 hours apart (2,3). However, recent trials have indicated that LNG (total 1.5 mg) has fewer side-effects and is more efficacious than the Yuzpe regimen (3).

If a new contraceptive technology is to become a viable option for decreasing unintended pregnancies, women must be willing to use the method and find it acceptable. However, because emergency contraceptive pills (ECPs) have not been widely available, little is known about this method's acceptability by the users. Studies have indicated that accessing and knowing about ECPs does not necessarily mean that they will be used (4,5).

Fear of side-effects influences acceptability and utilization of contraceptives (6,7). Although the theoretical efficacy of several contraceptive methods is similar, the side-effects can vary among users and

Correspondence: Josaphat K. Byamugisha, Makerere University Faculty of medicine, Department of Obstetrics and Gynecology, P.O. Box 7072, Kampala, Uganda. E-mail: byamugisha2001@yahoo.com

(Received 6 June 2009; accepted 10 January 2010)

ISSN 0001-6349 print/ISSN 1600-0412 online
DOI: 10.3109/00016341003611220

affect compliance as well as effectiveness. International studies on EC have shown that women of different nationalities experience and report symptoms differently (8–10).

The available EC methods in Uganda include the combined contraceptive pills (COCs), the progestin only pills (POPs) and the copper-IUD. The most frequently prescribed and thus used EC method in Uganda at present are the COCs (the Yuzpe regime) (11).

The objective of the study was, therefore, to determine side-effects and acceptability of the established Yuzpe regimen and the new and more effective LNG regimen among users in Kampala, Uganda.

Material and methods

The study was carried out from March 2005 to December 2006 in four clinics in Kampala, Uganda, which offer counseling and provision of family planning, counseling about HIV and sexually transmitted infections (STIs) services.

Inclusion criteria for the study were: unprotected sexual intercourse within the last 72 hours, request for EC, not being pregnant and accepting to come for review after three days and to be contacted for follow-up. Women who met the inclusion criteria and agreed to participate were randomized to one of two study groups. One group received the Yuzpe regimen which was the method used as standard EC in all the sites at the time of the study (2005/2006). Four tablets (ethinyl estradiol 0.03 mg and norgestrel 0.3 mg/tablet (Lofemenal®)) were taken directly and another four were taken after 12 hours. The other group received LNG 1.5 mg tablets as a single dose.

The EC pills were packed in white opaque envelops, which were numbered at the time of printing according to computer generated block randomization. One could not easily feel the tablets through the envelopes. An independent person not involved in the trial packed the tablets. The packages had labels with instructions for use.

The clients were asked to swallow the pills within 30 minutes after leaving the clinic. The reasons were to ensure uniformity and to keep the treatment blinded to the staff. Prior to the trial, an initial pilot study was conducted at the study sites to establish the practicalities of conducting the study. When the clients came back for follow-up they were interviewed by a non-medical, specifically trained research assistant.

A questionnaire with closed and open ended questions exploring demographic characteristics and previous use of ECPs was used. There were specific questions about any side-effects experienced by the women such as vomiting, nausea, fatigue, and headache. The side-effects were graded on a Likert scale ranging from 1 (mild) to 5 (severe) as indicated in Table 1.

Addendum questions were given to the clients after one to one and half years from the time the pills were used. These questions included use of other contraceptives and recommendation of ECPs to other users. Telephone interviews were conducted from September to November 2006. Each interview would last between 8 and 14 minutes.

The study was approved by the Department of Obstetrics and Gynecology, Faculty of Medicine higher degrees research and ethics committee, National Council for Science and Technology and the resident district commissioner, Kampala district. Consent was obtained from the heads of the various clinics. Informed written consent was obtained from all participants prior to inclusion in the study.

Sample size

The main outcome variables were side-effects and acceptability of ECP. The sample size was calculated using published estimates of a 40% prevalence (P) of side-effects of the Yuzpe regimen. The sample size formula used was $2N = 4P(1 - P)(Z_\alpha + Z_\beta)^2/\delta^2$ (12), where Z is the value on the x-axis of the standardized normal distribution curve, α is the probability corresponding to the occurrence of the critical value of

Table 1. The Likert scale that was used to assess side-effects.

	Side-effect	Mild									Severe
a.	Nausea	☐	1	☐	2	☐	3	☐	4	☐	5
b.	Vomiting	☐	1	☐	2	☐	3	☐	4	☐	5
c.	Bleeding	☐	1	☐	2	☐	3	☐	4	☐	5
d.	Dizziness	☐	1	☐	2	☐	3	☐	4	☐	5
e.	Fatigue	☐	1	☐	2	☐	3	☐	4	☐	5
f.	Headache	☐	1	☐	2	☐	3	☐	4	☐	5
g.	Pain in calf muscles	☐	1	☐	2	☐	3	☐	4	☐	5
h.	Others [specify]	.....									
		.....									

Z and β is the type II error, and δ is the difference in outcome between the two arms.

It was assumed that the randomization strategy would allocate an equal number of participants to each group. The level of significance was set at 0.05 for a 95% confidence interval. To achieve 80% power 167 participants were needed for each group. To cater for incompletely filled out questionnaires and for loss to follow up 354 women were recruited (Figure 1).

All filled out questionnaires were checked for completeness. Responses from open ended questions were coded. The computer program Epidata 3.1 was used for data entry and the data were exported to Stata version 9.2 for analysis. Consistency and range checks were made and errors were corrected in Epidata before exporting the data.

Data analysis

The main outcome variables were side-effects and acceptability of ECPs. Key independent variables included socio-demographic characteristics, having discussed with the partner before reporting for EC, previous use of contraceptives including ECPs, history of having worries about ECPs and having been pregnant before. Analysis involved descriptive statistics and inferential statistical analysis like cross-tabulations. Pearson's chi-squared tests were used to examine the bivariate relation between the effects in the two groups. Binary logistic regression was used to explore possible relations between the side-effects of the two regimens and acceptability with the rest of the variables. The variables for the logistic regression included ever used contraceptive methods, religion, having worries about the method and discussing with the partner before reporting for ECP.

Variables that were not related to either exposure (drug) or outcome (side-effect and acceptability) were not included in the multivariate analysis (controlled for in the analysis). An alpha of 5% was used as the cut-off point. Two researchers analyzed all statements and description of the codes from the open ended questions, a comparison of the categories by the two researchers showed good agreement.

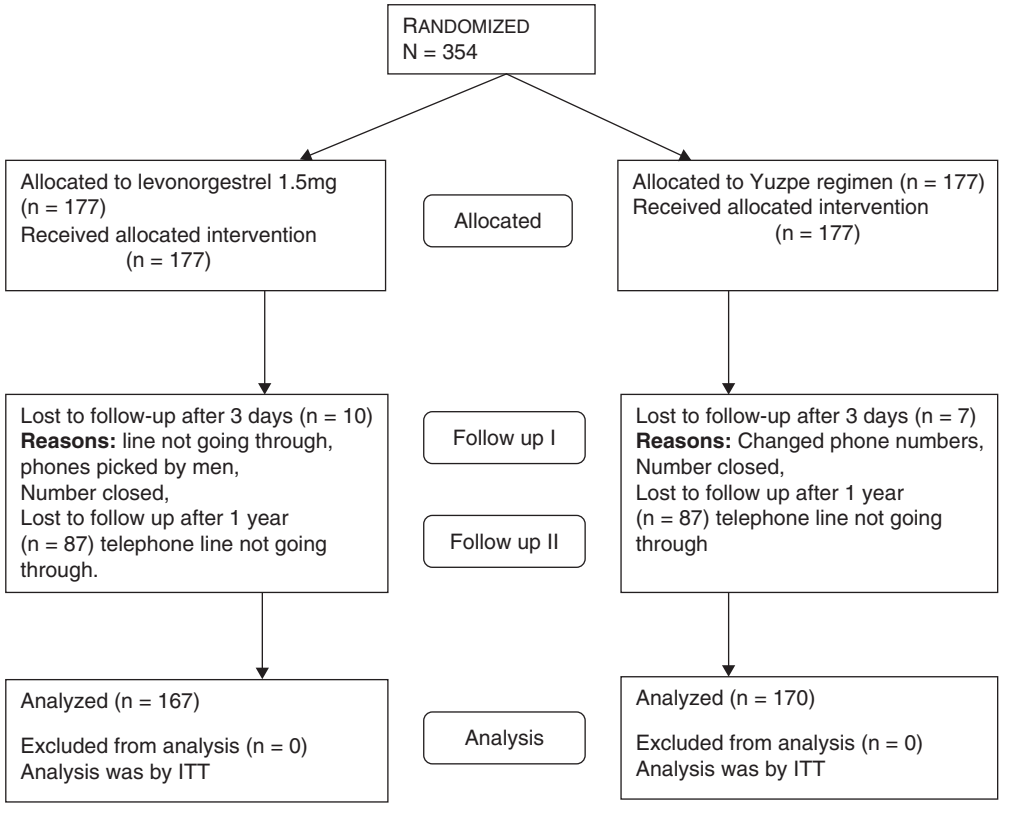

Figure 1. Patient flow through the randomized clinical trial. Note: ITT, intention to treat.

Results

A total of 337 women participated in the study (Table 2). No adverse events were recorded. The average age of the participants was 22 years while that of their sex partners was 28 years. The mean age of coitarche was 18 years (range 9–26). The mean time for reporting to the clinic after sexual intercourse was 26.6 hours. Among the participants 35% (57/163) reported having ever been pregnant.

Most of the participants (81%) were prime ECP users. The most common reason (38%) for using ECP was unprotected sexual intercourse (Table 3). The reasons given for this were: wanted 'live sex', no condoms available, forgot to use condoms and was drunk. Forgetting to take the conventional pills was the other major reason given, followed by condom accidents and rape.

Side-effects were experienced in both groups (Table 4) but were significantly more common in the group receiving the Yuzpe regimen compared to the LNG treatment (71.9 vs. 53.3%) ($p < 0.001$). The severity of the side-effects also seemed to be more pronounced in the Yuzpe group.

Most of the clients (88.3%) said they would use ECP again if there was a need (Table 5). Those who did not want to use EC again cited fear of side-effects as the major reason, limited time within which the

Table 2. Participants' characteristics in the levonorgestrel and Yuzpe groups.

Characteristic	Levonorgestrel % (n = 167)	Yuzpe (n = 170)	χ^2 p-value
Religion			
Anglican	35.9	35.9	$\chi^2 = 0.60$
Catholic	28.1	27.1	$p = 0.90$
Muslim	24.0	22.4	
Others	12.0	14.7	
Marital status			
Married	45.8	27.4	$\chi^2 = 22.5$
Single	42.2	54.8	$p < 0.001$
Cohabiting	12.1	10.7	
Separated	0.0	7.1	
Highest education			
None/up to primary 4	9.0	3.6	$\chi^2 = 5.4$
Primary 5–7	12.1	11.2	$p = 0.15$
Secondary school	44.0	42.6	
Tertiary education	34.9	42.6	
Occupation/status			
Student	31.7	44.7	$\chi^2 = 7.5$
House wife/unemployed	32.9	22.9	$p = 0.11$
Professional	15.2	13.5	
Unskilled	6.7	4.7	
Self-employed	13.4	14.1	
Unemployed	13.4	12.6	
Age			
Mean (SD) age in years	22.1 (3.52)	22.2 (3.46)	ANOVA F-value 0.12 $p = 0.72$

Follow-up visits after three days and one year

	n	%	n	%	p
After three days					
Ever used contraceptives	122/166	73.5	109/170	64.1	0.064
Had worries about the ECPs	61/157	38.9	81/164	49.4	0.057
Discussed with partnerbefore seeking ECPs	75/157	47.8	98/166	59.0	0.042
Believe that ECP increase STIs	75/152	49.3	79/162	48.8	0.919
After one year					
Intended to use another method of contraception	70/79	88.6	68/83	81.9	0.232
Ever been pregnant prior to use of ECPs	26/80	32.5	31/83	37.4	0.516
Fear of pregnancy more than STIs	16/74	21.6	30/81	37.0	0.036
Got pregnant	7/90			14/83	

Note: ECP, emergency contraceptive pill; SD, standard deviation; STI, sexually transmitted infection.

Table 3. Reasons for seeking emergency contraceptive pills.

	LNG % (n = 73)	Yuzpe % (n = 80)	Total % (n = 153)
No contraceptive method used	35.6	40.0	37.9
Forgot pills	24.7	32.5	28.8
Condom accident	26.0	17.5	21.6
Rape	8.2	3.8	5.9
Miscounted days	0.0	2.5	1.3
Failed withdrawal	0.0	1.3	0.7
Missed DMPA	1.4	0.0	0.7
Others	4.1	2.5	3.3

Note: DMPA, Depot MedroxyProgesterone Acetate; LNG, levonorgestrel.

Table 4. Median scores of side-effects recorded on a Likert scale as experienced by participants.

Side-effects experienced	Levonorgestrel median (IQR)	Yuzpe median (IQR)
Nausea	1 (1–3)	3 (2–3)
Vomiting	1 (1–2)	2 (1–3)
Dizziness	1 (1–2.5)	2 (1–3)
Headache	1.5 (1–3)	2 (1–3)
Fatigue	2 (1–3)	2 (1–3)
Bleeding	1 (1–3)	2 (1–2)

Note: IQR, inter quartile range.

method is effective, difficulty encountered in swallowing the pills, fear of drugs, and cost.

The majority of participants (91.3%) wanted ECPs available over the whole country. Those who opposed this gave the following reasons; risk of immorality, fear of side-effects, not user-friendly and not enough information available about ECPs. Reasons given for recommending the method for use by other clients included effectiveness against pregnancy (53%) and no side-effects (52.6%). There was no significant relation between religion and EC acceptability or recommendations.

There was a significant association between having worries about the method and experiencing side-effects (p = 0.000) (Table 5). The most common worries mentioned were fear of side-effects (55%) and uncertainty about the effectiveness (36.6%) of the method. Other reasons included fear that another person would find out (parent or boy friend), too many tablets to swallow and fear of STIs. Results in Table 6 show that after controlling for education and ever use of contraceptives, having worries increased the likelihood of having side-effects by a factor of 3.5, suggesting a strong independent effect of having worries on side-effects.

The majority of the participants (85.2%) indicated that they would want to use another method of contraception in the future. A third (37.3%) indicated the condom followed by COC (22.2%) and depot medroxy progesterone acetate (11.9%). Other methods mentioned included the rhythm method, norplant, intrauterine contraceptive device, progestin only pills, or diaphragm.

A total of 21 women reported a pregnancy (12.9%) following the cycle of ECP use. All these women reported having had further acts of unprotected sexual intercourse in the same cycle.

Discussion

Our findings agree with several other studies that the side-effects are more marked with the Yuzpe regimen than with LNG-only pills (3,13,14). However, there are differences in the percentage of the side-effects experienced. In present study LNG side-effects were higher than in the WHO multicentre trial (28.7 vs. 14%) (10). Furthermore, nausea was experienced by a higher percentage in the LNG group than in the Yuzpe group. Nausea in the Yuzpe regimen was similar to that reported in studies in San Diego

Table 5. Acceptability and recommendation of emergency contraceptive pills (ECPs).

	Treatment regimen		
Acceptability/recommendations characteristic question	LNG, n (%)	Yuzpe, n (%)	p
Would use ECPs again if there was a need	77/80 (96.2)	67/83 (80.7)	0.002
Would recommend ECPs for use by other clients	75/79 (94.9)	70/79 (88.6)	0.148
Want ECPs to be available over the whole country	74/80 (92.5)	73/81 (90.1)	0.593
Age groups who could use ECPs			
10–14 years	1 (1.3)	2 (2.4)	
15–17 years	14 (17.5)	14 (17.1)	
≥18 years	15 (18.7)	10 (12.2)	
All age groups	30 (37.5)	15 (18.3)	
Others	20 (25.0)	41 (50.0)	
Total	80 (100)	82 (100)	

Note: ECP, emergency contraceptive pill; LNG, levonorgestrel.

Table 6. Bivariate and multivariate logistic regression of having side-effects and having worries, education, and ever used contraceptives.

	Bivariate		Multivariate	
Variables	OR	95% CI	OR	95% CI
Having worries	2.69	1.67–4.35	3.46[a]	2.06–5.82
Education				
None/primary 4	1		1	
Primary 5–primary 7	0.56	0.17–1.85	0.71	0.20–2.46
Secondary	0.59	0.20–1.70	0.66	0.22–2.01
Tertiary	0.42	0.15–1.24	0.36	0.12–1.09
Ever used contraceptives				
Yes	1		1	
No	0.85	0.53–1.38	0.69	0.41–1.17

[a]$p < 0.001$.

(28.1 vs. 33.6%) (15), but lower than in the WHO trial (50.5%) (3). This finding could be because of differences in the sample size, but also to a difference in the way side-effects are experienced in different populations. Spotting was also more frequently reported than has been shown in previous studies (16,17).

Acceptability of both ECP regimens was high as measured by readiness and recommendation to use the assigned ECPs. The high acceptability irrespective of regimen could be because most women (81%) were prime users of EC and had no previous experience with various ECP regimens. Acceptability was not influenced by religion of the users. Similar findings were reported in a study on Latino women. In that study acceptability depended on the presumed EC mechanism of action rather than religious background (18).

There was a significant association between having worries about the method and experiencing the side-effects. This relation underscores the importance of information on ECP which should also include contraceptive counseling. Information on EC should also be offered to providers. Previous studies have indicated that clients and providers may have a lot of concerns about EC (19–21). In line with studies done elsewhere (22–24) most of the participants indicated their intention to use contraception in the future.

LNG is currently available in different formulations in the country. To add up to the required 1.5 mg of LNG 40 pills of the available POPs are needed. This big number of pills may scare off potential users. However, more recently 1.5 mg tablets for single dose use have become available. LNG has previously shown higher efficacy and the present study has confirmed a lower rate and less pronounced side-effects. LNG is thus a superior option to the Yuzpe regimen and should be promoted as the recommended ECP in Uganda. Due to a high rate of further unprotected sexual intercourse after ECP use counseling on regular and more effective contraceptive methods should be provided at the time of ECP provision.

Acknowledgements

We acknowledge the authors, the research assistants and the study sites for cooperation. The levonorgestrel tablets were supplied by HRA Pharma Laboratorie, Paris, France. We thank Sida/SAREC for supporting the research.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M, et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. Obstet Gynecol. 2006;108:1089–97.
2. Cheng L, Gulmezoglu AM, Oel CJ, Piaggio G, Ezcurra E, Look PF. Interventions for emergency contraception. Cochrane Database Syst Rev. 2004:CD001324.
3. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. Task Force on Postovulatory Methods of Fertility Regulation. Lancet. 1998;352:428–33.
4. Lo SS, Fan SY, Ho PC, Glasier AF. Effect of advanced provision of emergency contraception on women's contraceptive behaviour: a randomized controlled trial. Hum Reprod. 2004;19:2404–10.
5. Petersen R, Albright JB, Garrett JM, Curtis KM. Acceptance and use of emergency contraception with standardized counseling intervention: results of a randomized controlled trial. Contraception. 2007;75:119–25.
6. Heinemann LA, Thiel C, Assmann A, Mohner S. [Frequency and reasons for switching/stopping use of oral contraceptives. Results of the German Cohort Study on Women Health]. Zentralbl Gynakol. 2001;123:568–77.
7. Sable MR, Libbus MK. Beliefs concerning contraceptive acquisition and use among low-income women. J Health Care Poor Underserved. 1998;9:262–75.
8. Dunson TR, McLaurin VL, Aguayo EL, de Silva P, Calventi V, Gerais AS, et al. A multicenter comparative trial of triphasic and monophasic, low-dose combined oral contraceptives. Contraception. 1993;47:515–25.
9. Blanchard K, Haskell S, Ferden S, Johnstone K, Spears A, Evans M, et al. Differences between emergency contraception users in the United States and the United Kingdom. J Am Med Womens Assoc. 2002;57:200–3.
10. von Hertzen H, Piaggio G, Ding J, Chen J, Song S, Bartfai G, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet. 2002;360:1803–10.
11. Byamugisha JK, Mirembe FM, Faxelid E, Gemzell-Danielsson K. Knowledge, attitudes and prescribing pattern of emergency contraceptives by health care workers in Kampala, Uganda. Acta Obstet Gynecol Scand. 2007;86:1111–6.

12. Lawrence M.F CDF, David L.D. Fundamentals of clinical trials, 3rd edn. New York: Springer, 1998.
13. Ellertson C, Webb A, Blanchard K, Bigrigg A, Haskell S, Shochet T, et al. Modifying the Yuzpe regimen of emergency contraception: a multicenter randomized controlled trial. Obstet Gynecol. 2003;101:1160–7.
14. Sarkar NN. Levonorgestrel as an emergency contraceptive drug. Int J Clin Pract. 2003;57:824–8.
15. Harvey SM, Beckman LJ, Sherman C, Petitti D. Women's experience and satisfaction with emergency contraception. Fam Plann Perspect. 1999;31:237–40.
16. Webb A, Shochet T, Bigrigg A, Loftus-Granberg B, Tyrer A, Gallagher J, et al. Effect of hormonal emergency contraception on bleeding patterns. Contraception. 2004;69:133–5.
17. Raymond EG, Goldberg A, Trussell J, Hays M, Roach E, Taylor D. Bleeding patterns after use of levonorgestrel emergency contraceptive pills. Contraception. 2006;73: 376–81.
18. Romo LF, Berenson AB, Wu ZH. The role of misconceptions on Latino women's acceptance of emergency contraceptive pills. Contraception. 2004;69:227–35.
19. Josaphat K Byamugisha, Florence M Mirembe, Kristina Gemzell-Danielsson and Elisabeth Faxelid Faced with a Double-Edged Risk: Ugandan University Students' Perception of the Emergency Contraceptive Pill in Uganda. Afr J Reprod Hlth. 2009;13:47–59.
20. Ziebland S, Graham A, McPherson A. Concerns and cautions about prescribing and deregulating emergency contraception: a qualitative study of GPs using telephone interviews. Fam Pract. 1998;15:449–56.
21. Norris Turner A, Ellertson C. How safe is emergency contraception? Drug Saf. 2002;25:695–706.
22. Ziebarth A, Hansen KA. Hormonal emergency contraception: a clinical primer. S D Med. 2007;60:99–101.
23. Walker DM, Torres P, Gutierrez JP, Flemming K, Bertozzi SM. Emergency contraception use is correlated with increased condom use among adolescents: results from Mexico. J Adolesc Hlth. 2004;35:329–34.
24. Ellertson C, Ambardekar S, Hedley A, Coyaji K, Trussell J, Blanchard K. Emergency contraception: randomized comparison of advance provision and information only. Obstet Gynecol. 2001;98:570–5.