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Emergency Contraception: More To Know, More To Adopt: A Review Article

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Abstract

Emergency contraception has been available for more than 30 years to prevent unplanned pregnancies. There is a significant unmet need of contraception, besides, contraceptive failure can also result in unwanted pregnancies leading to increase in number of induced abortions globally. Offering emergency contraception is an important service intervention for reducing the unmet needs of contraception. Women risk their lives to terminate an unwanted pregnancy or to carry it to term. Here, comes the importance of ECs. Emergency contraceptives are methods that can be used to prevent unwanted pregnancy if they are used within specified time. Awareness of EC has been spread well by the media and Government efforts , but an unmet need is still prevailing about the education of people about its correct use. It is imperative to formulate plans for disseminating its knowledge more through health workers and health facilities and try to educate the people about ECs. This article is mainly aimed to give a brief yet required information regarding available emergency contraceptives.

Keywords: Abortion, Emergency Contraception, Unmet need

INTRODUCTION

Emergency contraception has been available for more than 30 years to prevent unplanned pregnancies. There is a significant 'unmet need' of contraception, besides, contraceptive failure can also result in unwanted pregnancies leading to increase in number of induced abortions globally. Offering emergency contraception is an important service intervention for reducing the unmet need of contraception. Women risk their lives to terminate an unwanted pregnancy or to carry it to term. Here, comes the importance of ECs. Emergency contraceptives are methods that can be used to prevent unwanted pregnancy if they are used within a specified time (1). They are also known as postcoital contraception or "morning–after" pills if they are oral tablets. This article is mainly aimed to give a brief yet required information regarding available emergency contraceptives

NEED FOR EC IN INDIA

Despite a National Family Welfare Programme and wide-spread efforts by the Government, India has crossed a population of one billion. Globally, 20 million illegal abortions take place every year and out of this 97% occur in developing countries (2). In India, 78% of the pregnancies are unplanned and at least 25% are unwanted. Every year 11 million abortions take place and at least half of these are unsafe and associated with a high morbidity and mortality. In spite of abortions being legalized since 1971, there are still 10-11 illegal abortions for each legal abortion. This accounts for 15,000 to 20,000 abortion-related deaths annually and a high associated morbidity, almost all of which is preventable (3).This emphasizes the need for strengthening the already existing framework in order to increase the acceptability and

use of various contraceptive methods along with an additional 'back-up' method whenever the regular method fails.

EC was approved by the Drug Controller General of India (DCGI) in September 2001, permission was granted for manufacture of levonorgestrel (LNG) and social marketing on prescription and the drug was made available in the country in January 2002. ECP has been introduced in the national programme in 2003. This is also distributed under ASHA scheme of Home Delivery of Contraceptives. Therefore, ECP is available as 'Free' and 'ASHA' supply under the programme. It was made an over the counter (OTC) drug in 2005.

There were several challenges for introducing EC in India, including the size and diversity of the country and poor awareness of both users and providers. In spite of introduction of EC in government supply for almost over a decade, its knowledge still remains poor (4). Awareness of EC has been spread well by the media and Government efforts, but an unmet need is still prevailing about the education of people of its correct use. It is imperative to formulate plans for disseminating its knowledge more through health workers and health facilities and try to educate the people about EC.

INDICATIONS FOR USE OF EMERGENCY CONTRACEPTIVES

EC is for occasional use, to reduce the risk of pregnancy after unprotected sexual intercourse (UPSI). It does not replace effective regular contraception and it should not be used as abortifacient. Indications include -unprotected exposure (sexual assault, rape) -contraceptive accidents with miscalculation of safe period, failed coitus interruptus, condom rupture or slippage, late insertion of spermicide.- After regular hormonal contraception has been compromised or used incorrectly. - pill forgotten for two consecutive days or pill free interval of nine or more days between packets, more than 27 hours delay in taking traditional POP & >36 hrs since desogesterol, delay of progestin injectable contraceptive injection by 2 wk, combined hormonal transdermal patch detachment for >48 hours, expired implant, failure to use additional contraceptive while using liver enzyme inducing drugs and -expelled or misplaced IUD.

EC should be considered if a woman does not wish to conceive and has had UPSI:

On any day of a natural menstrual cycle. Pregnancy is theoretically possible after UPSI on most days of the cycle. However, risk of pregnancy is highest after UPSI that takes place during the 6 days leading up to and including the day of ovulation.

From Day 21 after childbirth unless all criteria for lactational amenorrhoea are met.

From Day 5 after miscarriage, abortion, ectopic pregnancy or uterine evacuation for gestational trophoblastic disease (5).

EMERGENCY CONTRACEPTIVE METHODS

Among the various ECs the first to be described was the Yuzpe regimen comprising two doses of 100 mg ethinylestradiol with 0.5 mg levonorgestrel (LNG) with the first dose taken within 72 h of unprotected intercourse and repeated after 12 h (6). Yuzpe regimen has been discontinued in most countries because of lesser efficacy than LNG and risk of venous thromboembolism and unpleasant side effects due to high estrogen content (7). However, if other methods are not available, the regimen can be mimicked by taking a number of combined oral contraceptive pills (8–10 depending on the brand) which are easily available. This method has not been discussed much here.

The most widely used emergency contraception is progestin-only pill which contains levonorgesterel. It can be taken either as a single dose of 1.5mg or in two 0.75 mg doses 12 h apart. Studies have shown that single dose is as effective as 2 doses 12 hours apart. Single dose regimen has become the preferred regimen in view of better compliance (8). This can be purchased over the counter and is labeled for use upto 72 hours after unprotected sex but is best used as soon as possible after unprotected sex (9).

Ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM), was first marketed for EC as a single dose of 30 mg in Europe in 2009 (as EllaOnew; HRAPharma, Paris) and in the USA in August 2010 (as Ellaw; Watson Pharmaceuticals). It is effective upto 120 hours after unprotected sex.The SPRM Mifepristone (10–25 mg) is used as an

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emergency contraceptive in China, Vietnam, Russia and in the Ukraine.

The copper intrauterine device (IUD) is the most effective method of EC although FDA has not labeled it for this indication. It is the only method of EC which is effective after ovulation (but is inserted well before the earliest likely date of implantation so that it does not disrupt a pregnancy that has already implanted). It is inserted up to 5 days after intercourse or up to 5 days after the earliest estimated day of ovulation but in some studies was used up to 10 days afterward without failure (10). The major disadvantage of IUD for EC is that insertion requires technical expertise and clinical facilities. A major advantage, however, is that the woman can choose to keep the device as ongoing, long-acting reversible contraception. Secondly , it is not known to be affected by body mass index (BMI)/weight or by other drugs.

The LNG-IUD (Mirena) is presently not recommended for EC, however, studies are underway to determine its efficacy.

Table 1. Available methods of Emergency Contraception

Regimen	Recommended dose or use	Timing of use after UPSI	Access	FDA labeled for use as EC
Combined progestin-estrogen pills	2 doses of 100 mg EE+0.5mg LNG	Upto 5 days	Requires prescription	No
Levonorgestrel (Progestin only)	1.5mg LNG single oral dose or 2 tablets of 0.75mg LNG each	Licensed for use within 72 hours after UPSI or contraceptive failure	Available over the counter	Yes
Ulipristal acetate (Selective progesterone receptor modulator)	30 mg single oral dose	Licensed for use within 5 days (120 hours) after UPSI or contraceptive failure	Requires a prescription	Yes
Copper IUD	IUD retained until pregnancy excluded or can be kept for ongoing contraception	Within 5 days (120 hours) after the first UPSI in a cycle or within 5 days after the earliest estimated date of ovulation	Requires insertion by clinician	No

*A double dose (3 mg) of LNG-EC is recommended if a woman is taking an enzyme-inducing drug and if a woman has a body mass index >26 kg/m2 or weight >70 kg

PHARMACOKINETICS

Levonorgestrel does not undergo first–pass metabolism and has 100% bioavailability (11). Hence, effective when given orally. After a single dose of LNG, maximum plasma concentration of 19.1ng/mL was reached at a median of 1.7 hours (range 1–4 hrs). Studies have shown that the apparent volume of distribution (Vd) of LNG is approximately 1.8 L/kg. The elimination half-life of LNG after single dose administration (0.75 mg) was 27.5+5.6 hours.These pharmacokinetic parameters facilitate the single and 12-hour dosing of LNG. Levonorgestrel is highly

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protein bound (97.5 to 99%), mainly to the sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Approximately 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates (11).

Ulipristal is rapidly absorbed after a single 30 mg dose is administered orally. Peak plasma concentration of 176 ± 89 ng/ ml occurs approximately 0.5–3hours after oral ingestion (12). Ulipristal is highly bound to plasma proteins (>98%) including albumin, high-density lipoproteins, and alpha-1- acid glycoprotein. It is extensively metabolized in the liver via the CYP3A4 pathway. The main metabolites are monomethylated and did methylated metabolites. The monomethylated metabolite is pharmacologically active. The terminal half-life of ulipristal in plasma is 32.4 ± 6.3 hours (13).

MECHANISM OF ACTION

Sperm are viable in the female genital tract for about 5 days after UPSI (14, 15). If ovulation occurs within those 5 days, fertilization could take place and a woman is at risk of pregnancy. A judicial review (16) in 2002 concluded that pregnancy begins at implantation. Hence, any intervention given for EC must act either to prevent fertilization or to prevent implantation, rather than by disrupting established implantation. Available data shows that the shortest time from ovulation to implantation is 6 days (although usually longer – over 80% of pregnancies implant 8–10 days after ovulation (17).

Combined ECPs work by inhibiting implantation of fertilized egg (18). Other postulated mechanisms include delaying or suppressing ovulation, interfering with corpus luteum function and making changes in the endometrium that prevents implantation (19-21).

LNG and UPA oral emergency contraceptives act by delaying or inhibiting ovulation but their efficacy in doing so varies according to the stage of the cycle when EC is used (22).

LNG-EC inhibits ovulation, delaying or preventing follicular rupture and causing luteal dysfunction. LNG can inhibit ovulation in 96% of cycles if it is given in the presence of an ovarian follicle measuring 12– 17 mm in diameter and before the start of LH surge (23). When UPA is given before the start of the LH surge follicle rupture is delayed or inhibited in 100% of cycles (23). UPA remains reasonably effective even if given after the LH surge has started, delaying ovulation in 79% of cycles at this time .Recent studies show that UA may inhibit human sperm hyperactivation as well as ciliary beating and muscular contraction in the fallopian tube (24). It may alter endometrial receptivity, exerting an anti-implantation effect as well as altering tubal and sperm functions (25).So, it explains the superior efficacy of UPA over LNG . Once LH has reached its peak UPA, like LNG, no longer has any effect on ovulation.

Importantly, after UPA-EC and LNG the majority of women will ovulate later in the cycle (26) and are therefore at risk of pregnancy from subsequent UPSI (27). It is essential that women are made aware of this risk and advised regarding ongoing contraception .

Another SPRM Mifepristone may inhibit endometrial receptivity and tubal contractility (28). It does have an effect on the endometrium and can both inhibit implantation and induce abortion.

The primary mechanism of contraceptive action of the Cu-IUD is inhibition of fertilization by its toxic effect on sperm and ova. Copper has been shown to adversely affect the motility and viability of sperm and the viability and transport of ova. If fertilization does occur, the local endometrial inflammatory reaction resulting from the presence of the Cu-IUD prevents implantation (29). The Cu-IUD therefore has both pre- and post-fertilization mechanisms of action. This additional effect helps to explain the superior efficacy of the IUD for EC. Cu- IUD can be inserted upto 5 days after the first UPSI in a cycle. Cu-IUD can also be inserted up to 5 days after ovulation, before the process of implantation has begun.

Ovulation occurs about 14 days prior to onset of menstruation (30). It is established practice that the earliest likely ovulation date is estimated as the date of the start of the LMP plus the number of days in the shortest cycle minus 14. LMP must be accurately known and cycles must be regular in order to make the estimation. A Cu-IUD can be inserted for EC in good faith up to 5 days after this date (e.g. until Day 19 of a regular, 28-day cycle).

EFFICACY

Efficacy is estimated by comparing the number of pregnancies that actually occur among a group of

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women who have used EC with the number of pregnancies that would have been expected to occur had EC not been used (31).The Yuzpe regimen of emergency contraception is reported to be 97% to 98% effective in preventing pregnancy (32).LNG has been shown to prevent 74–93% of expected pregnancies .Compared with LNG, UPA almost halved the risk of pregnancy among women treated within 5 days of intercourse. There is lower pregnancy rate of 1.4% among UPA users as compared to 2.2% in LNG users. Ulipristal maintains consistent effectiveness up to 5 days (120 hours) after unprotected intercourse, while the effectiveness of levonorgestrel declines when given more than 48 hours after unprotected sexual intercourse (33,34). Within 72 hours of unprotected sex, ulipristal is estimated to be 98.2% to 99.1% effective (35). Within 72 to 120 hours, ulipristal is more effective than levonorgestrel-dose mifepristone (25–50 mg) or low-dose mifepristone (25 mg) were both significantly more effective than LNG, but the significance was marginal if only high-quality studies were considered . Low-dose mifepristone was less effective than mid-dose mifepristone .The Cochrane review (36) concluded that the copper IUD was the most effective EC method with pregnancy rate of < 0.1%.

CHOOSING BETWEEN UPA AND LNG

The evidence suggests that LNG-EC is ineffective if taken more than 96 hours after UPSI. UPA-EC is therefore the only oral EC that is likely to be effective if UPSI took place 96–120 hours ago.

Between 0 and 96 hours after UPSI

The decision as to whether UPA-EC or LNG-EC is most appropriate depends on the following factors:

1 **The risk of pregnancy from the UPSI for which EC is being taken**. If UPSI is likely to have taken place during the 5 days prior to ovulation, risk of pregnancy is very high and UPA-EC should be considered first-line oral EC.

2 **The risk of pregnancy resulting from further UPSI if there is a delay in commencing ongoing contraception.** The ability of UPA-EC to delay ovulation is reduced if a progestogen is taken in the following 120 hours. It is therefore recommended that hormonal contraception is not started until 5 days after UPA-EC, whereas hormonal contraception can be started immediately after LNG-EC. If pregnancy risk from UPSI that has already taken place is low, it may be appropriate to prioritise immediate quick start of contraception so that pregnancy risk from further UPSI is reduced. LNG-EC with immediate start of hormonal contraception could be considered in this situation.

3 **Recent use of progestogen.** The effectiveness of UPA-EC (but not LNG-EC)could be reduced if a woman has recently taken a progestogen (e.g. If she requires EC because of missed pills).

4 **BMI/body weight.** The effectiveness of LNG-EC could be reduced if a woman has a BMI >26 kg/m2 or weight >70 kg. It is recommended that either UPA-EC or a double dose (3 mg) of LNG-EC is given in this situation. It is unknown which is more effective.

5 **Enzyme-inducing drugs.** The effectiveness of both UPA-EC and LNG-EC could be reduced if a woman is using an enzyme inducer. It is recommended that a double dose (3 mg) of LNG-EC can be used, but effectiveness (and how this compares to UPA-EC) is unknown. Use of double-dose UPA-EC is not currently recommended.

6. If it is not possible to establish a likely date of ovulation or a **woman does not know** where she is in her cycle, use of UPA-EC should be considered.

7. **Perimenopausal women** who have used hormonal contraception incorrectly should be offered EC after UPSI. Sequential HRT is not contraceptive. Concomitant use of contraception or HRT could reduce the effectiveness of UPA-EC. So LNG-EC is preferred.

SIDE EFFECTS

Headache, Nausea & Vomiting-UPA and LNG have most frequent side effect of headache (19%) and nausea (12%). About 50% of women who take combined ECPs experience nausea and 20% vomit. If vomiting occurs within two hours after taking a dose, repeating that dose is also recommended.

Menstruation- Temporary disruption of the menstrual cycle is commonly experienced. Delay of menstruation for more than 7 days was significantly more common when UPA-EC was administered prior

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to ovulation than after ovulation (25).The majority of women menstruate within 7 days of the expected time after LNG-EC. Menstruation is delayed for over 7 days in fewer than 10% of women (37). If a woman's menstrual period is delayed by a week or more, she should go for a pregnancy test. Mifepristone, if taken before ovulation, may delay ovulation by 3-4 days (38).

Other minor side effects include abdominal pain, dysmenorrhoea, backache, breast tenderness, dizziness, and fatigue.

The side effects and safety of the IUD are the same for emergency as for routine use. Since women who have had unprotected sex may be at risk of sexually transmitted infections (STIs), or in individuals with recognized risk factors for STI, consideration should be given to simultaneous administration of appropriate antibiotics. There is a risk of perforation which is not greater than that associated with routine insertion. If the device is kept for ongoing contraception women should be warned about the risks of both expulsion of the device and heavy or prolonged menstrual bleeding.

EFFECT ON PREGNANCY

There is no evidence that either LNG or UPA result in an increased risk of miscarriage, ectopic pregnancy, fetal anomaly or complications during pregnancy or delivery (39).

EC AND ECTOPIC PREGNANCY

EC actually reduces the absolute risk of ectopic pregnancy by preventing overall pregnancy(40). Few studies suggested that amongst pregnancies resulting from failure of LNG-EC, the proportion that were ectopic rather than intrauterine could be higher than amongst pregnancies prior to which no EC had been used.

CONTRAINDICATIONS / RESTRICTIONS TO USE OF EC

Existing pregnancy is not a contraindication, as there is no known harm to the woman, her pregnancy, or the foetus.

-The WHO lists no medical condition for which the risks of emergency contraceptive pills outweigh the benefits (41).

-Progestin-only ECPs may be preferable to combined ECPs containing estrogen in women with a history of blood clots, stroke, or migraine, there is no medical conditions in which progestin-only ECPs are contraindicated. Current venous thromboembolism, current or past history of breast cancer, inflammatory bowel disease, and acute intermittent porphyria are conditions where the advantages of EC generally outweigh the theoretical or proven risks(41).

-In some studies, LNG and UPA are not recommended in patients with severe hepatic dysfunction (37). However, pregnancy poses a significant risk in women with severe hepatic impairment and expert opinion suggests that use of a single dose of LNG 1.5 mg or UPA 30 mg is therefore acceptable.

-Studies prohibit use of UPA in women with severe asthma controlled with oral steroids because of the antiglucocorticoid effect of UPA(5).

-Use of a Cu-IUD for EC carries the same contraindications as routine Cu-IUD insertion (42).

POTENTIAL INTERACTIONS/ FACTORS AFFECTING EFFECTIVENESS OF EC

Effectiveness of the Cu-IUD is not known to be affected by weight, BMI and concomitant use of drugs.

Studies have suggested that both LNG-EC and UPA-EC could be less effective in women who are overweight or obese than those with normal or underweight BMI (43). The reported negative effect of obesity on effectiveness of LNG-EC is greater than that on effectiveness of UPA-EC.

In a women weighing > 70 kg or with a BMI >26 kg/m2 if Cu-IUD is not acceptable, UPA-EC can be offered. If UPA-EC is not suitable, a double dose (3 mg) of LNG-EC can be used. Double dose of UPA-EC is not recommended. For women weighing >85 kg or with a BMI >30 kg/m2, it is not known whether UPA-EC or 3 mg LNG-EC is more effective.

Drugs that induce CYP450 and CYP3A4 enzymes may decrease the plasma concentrations of LNG and UPA leading to decreased effectiveness of both. These may include St. John's Wort, carbamazepine, rifampicin, phenytoin, and griseofulvin (44). The metabolism of both UPA-EC and LNG-EC is

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increased during and for 28 days after use of drugs that induce liver enzymes.

CYP3A4 inhibitors such as itraconazole , ketoconazole or clarithromycin may increase plasma concentrations of ulipristal (45) although clinical significance is uncertain.

Coadministration of levonorgestrel with HIV protease inhibitors or with nonnucleoside reverse transcriptase inhibitors has shown significant changes (increase or decrease) in the plasma levels of levonorgestrel.

EC may be indicated at the same time as post-exposure prophylaxis for sexual exposure to HIV (PEPSE). The current recommendation from the British Association for Sexual Health and HIV (BASHH) is that Truvada (tenofovir and emtricitabine) and raltegravir are given for PEPSE (46). This regimen contains no enzyme-inducing drugs that would reduce the effectiveness of oral EC.

Use of UA with antacids, PPI, H2 receptor antagonists or drugs that increase gastric ph may reduce absorption of UA hence efficacy.

Studies conducted in vitro showed that ulipristal may be an inhibitor of P-glycoprotein at clinically relevant concentrations.Therefore, it is not advisable to administer ulipristal with P-gp substrates (e.g., digoxin, colchicine, and fexofenadine) as it may increase the concentration of P-gp substrates (45).

EC providers should be aware that the effectiveness of UPA-EC could theoretically be reduced if a woman has taken progestogen prior to or after taking UPA-EC. Since ulipristal is an antiprogestin, using a progestin containing oral contraceptive immediately after ulipristal, reduces the efficacy and ability of ulipristal to delay ovulation (47, 48). This is because ulipristal and the progestin component of hormonal contraceptives both bind to the progesterone receptor. If a woman wants to use hormonal contraception after using ulipristal, she should wait for 5 days and should use a reliable barrier method until the next menstrual period (49). It is recommended that all products containing progestogen or progesterone [whether for contraceptive purposes, EC, gynaecological indications or hormone replacement therapy (HRT)] are avoided for 5 days after UPA-EC to avoid compromising the ability of UPA-EC to delay ovulation.

Adding the cyclo-oxygenase-2 inhibitor Meloxicam, which inhibits follicle rupture, has been shown to increase effectiveness of LNG (50) and would probably do the same if given in combination with UPA although this has not been tested.

ASSESSMENT BEFORE CONRACEPTION

Assessment should include date of last menstrual period (LMP), average length of menstrual cycle, time in hours since last act of unprotected intercourse, current or recent use of contraception, history of medical disorders, sexually transmitted disease or major illness. Physical examination is not necessary except when pregnancy is suspected. Laboratory tests include urine pregnancy test if pregnancy is suspected and tests for sexually transmitted diseases, if at risk. A pregnancy test should be considered if a woman has had UPSI earlier in the cycle. Pregnancy testing cannot reliably exclude pregnancy if there has been an episode of UPSI fewer than 21 days previously.

CONTRACEPTION FOLLOWING EC

Most modern guidelines recommends that women should start an effective method of contraception immediately after using EC (so-called ‘quick starting’)

-A Cu-IUD inserted for EC is immediately effective for ongoing contraception.

-EC providers should advise women that oral EC methods do not provide ongoing contraception. After oral EC there is a pregnancy risk if there is further UPSI and ovulation occurs later in the same cycle.

-After taking LNG-EC, it is, therefore,recommended that suitable hormonal contraception (CHC, POP, IMP or DMPA) should be quick started immediately with a pregnancy test 21 days later to exclude pregnancy resulting from EC failure.

-Women should be advised to wait 5 days after taking UPA-EC before starting suitable hormonal contraception. The GDG advises that CHC (except Qlaira), IMP and DMPA commenced 5 days after administration of UPA-EC will be effective 7 days after starting and POP 2 days after starting Women should be made aware that they must use condoms reliably or abstain from sex during the 5 days waiting and then until their contraceptive method is effective.

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It is currently recommended that the LNG-IUS should not be inserted unless pregnancy can be reasonably excluded.

SPECIFIC CONSIDERATIONS IN BREAST FEEDING

Insertion of a Cu-IUD is relatively contraindicated (51) in the postpartum period and during breastfeeding between 48 hours and 28 days after delivery because of the possible increased risk of uterine perforation and expulsion. However, the absolute risk of perforation remains low.

Breastfeeding women should be advised not to breastfeed and to express and discard milk for a week after they have taken UPA-EC (52).

Women who breastfeed should be informed that available limited evidence indicates that LNG-EC has no adverse effects on breastfeeding or on their infants (53-55).

CONCLUSION

EC methods are going to occupy a unique position in range of contraceptive choices currently available to Indian women as these are the only methods couples can use to prevent pregnancy after a contraceptive accident or unprotected sexual exposure. Easy accessibility to EC will make a huge difference in preventing unwanted pregnancies and deaths due to unsafe abortions. But without awareness easily accessible resource will be of no use. Hence more awareness and accessibility is needed.

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