

## Levonorgestrel: development of hormonal methods of emergency contraception

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## Emergency contraception -

Contraception administered to a woman after an unprotected intercourse

- intercourse unexpected
- failure of barrier method
- rape

## Emergency contraception

High doses of oestrogens for 5 days  
Diethyl Stilboestrol 25-50 mg per day  
Ethinyl oestradiol 5 mg per day  
Conjugated oestrogens 30 mg per day  
Pregnancy rates 0.6 – 1.6 %  
High incidence of nausea (>50%) and vomiting (>20%); concern about thromboembolism and ectopic pregnancy  
Seldom used nowadays

## Yuzpe Regimen

- 2 doses of combined pills (ethinyl estradiol 100 mcg & levonorgestrel 0.5 mg) at 12 hours interval
- 1st dose within 72 h of coitus
- High incidence of nausea (50%) and vomiting (20%)
- Failure rate around 0.2-5%

## Mifepristone (RU486)

- Orally active progesterone antagonist at receptor level
- Licensed in some countries for medical abortion
- Also affects ovulation and endometrium

## Comparison of mifepristone and Yuzpe regimen for EC

	Mifepristone (600 mg)	Yuzpe
n	589	597
No. of pregnancies	0 (0%)	9(1.5%)

Significant reduction in nausea and vomiting in mifepristone group but increase in delay of return of period

(Data from Glasier et al 1992, Webb et al 1992)

### Efficacy of 3 doses of mifepristone in emergency contraception (WHO 1999)

Dose	n	Pregnancy rate	Efficacy
10 mg	565	1.24	83%
50 mg	561	1.25	82%
600 mg	559	1.25	83%
Total	1685	1.25	83%

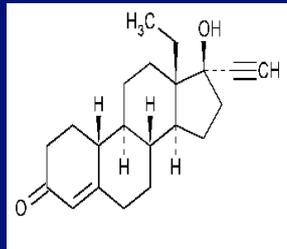
Delay in return of period less frequent with 10 mg gp

### Mechanisms of action of mifepristone (Marions et al 2002)

6 women given 10 mg of mifepristone before ovulation (follicle >12 mm)  
 Inhibited or delayed LH surge  
 When given after ovulation, the endometrium was slightly out of phase.  
 Effects on endometrial markers were less marked than 200 mg of mifepristone

### Levonorgestrel

Progestin derived from 19-nortestosterone  
 Levo rotatory and active component of norgestrel  
 Half-life 14 h  
 Suppresses level of SHBG  
 Metabolized and excreted in urine (2/3) and feces (1/3)



### Comparison of Yuzpe versus levonorgestrel (Ho & Kwan 1993)

PR	Yuzpe	Levonorgestrel
Number	424	410
Whole group	3.5%	2.9%
No further Coitus	2.7%	2.4%

2 doses of LNG 0.75 mg given 12 h apart within 48 h of coitus  
 Significant reduction in nausea & vomiting

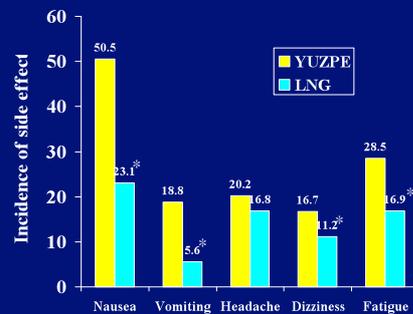
### Pregnancy rates

Group	Number of women	Observed pregnancies	Pregnancy rate (%)	95% CI
Yuzpe	979	31	3.2	(2.2, 4.5)
LNG	976	11	1.1	(0.6, 2.0)

Relative risk (RR) of pregnancy for LNG compared with Yuzpe:

RR	95% CI
0.36	(0.18, 0.70)

Yuzpe and LNG given within 72 h of coitus



## Levonorgestrel: mechanisms of action

Inhibition of ovulation when given before ovulation (80% when follicle 12-14 mm but only 12% when follicle 18 mm)

Minimal effects on endometrium (Marions et al 2002)

Increase in cervical mucus viscosity (Kesseru 1984)

Minimal effects on sperm functions (Yeung et al 2002)

LNG given post-ovulation more likely to fail than given pre-ovulation (Noe et al 2010)

## RCT comparing 2 intervals between 2 doses of LNG (Ngai et al 2005)

- Women requesting EC within 72 h of coitus were randomized to receive 0.75mg at 12 or 24 h intervals
- Efficacy of 2 regimens similar (RR 0.98; 95% CI 0.53-1.82)
- 24h interval seems to be more protective in those who had further acts of intercourse

## Single dose versus 2 doses of levonorgestrel (Cheng et al 2008)

- Cochrane database systematic review
- 2 RCT with 3830 women randomized to receive either 1.5 mg LNG or 2 doses of 0.75 mg 12 hr apart
- No significant difference in pregnancy rates (RR 0.77; 95% CI 0.45-1.3)
- As single dose is more convenient, it is the regimen of choice

## Mifepristone versus levonorgestrel (120 h)

WHO multicentre study with 4071 women

	<u>PR</u>	<u>%</u>
<u>prevented</u>		
Mifepristone	1.55%	81%
Single dose LNG	1.47%	82%
Two dose LNG	1.77%	77%
All LNG	1.62%	80%

No significant difference on PR or % of pregnancies prevented

## Interventions for EC

(Cheng et al 2011, Cochrane Library)

- Meta-analysis – 100 trials 55,666 women
- Mid-dose (25-50mg) or low dose (<25mg) mifepristone significantly more effective than LNG, but significance was marginal if only high quality studies were included (4 trials RR 0.7 95%CI: 0.49-1.01)
- Mifepristone low dose less effective than mid-dose but difference not significant if only high quality studies were included

## Mifepristone versus levonorgestrel in emergency contraception

- In both groups, pregnancy rates higher (a) when drug given between 72-120 h than when it was given within 72 h and (b) in those with further acts of intercourse
- Higher incidence of delayed period in the mifepristone group
- Mifepristone not widely available for EC and LNG more widely available

## Advantages of levonorgestrel

- Cheaper
- More widely available
- Can be obtained over the counter in many countries
- No evidence that there is increase in complications of pregnancies in case of failure (Zhang et al 2009)

## Effects of coitus treatment intervals on failure rates of LNG (Piaggio et al 2011)

Data from 4 WHO trials

Coitus-Rx intervals	PR	OR
0-24 h	1.0%	1
25-48 h	0.7%	0.68 (0.76-1.28)
49-72 h	1.6%	1.74 (0.94-3.19)
73-96 h	0.9%	0.87 (0.24-2.89)
97-120 h	5.2%	5.81 (2.87- 11.76)

## Effects of BMI on failure rates of LNG (Glasier et al 2011)

BMI (Kg/m <sup>2</sup> )	UPA	LNG
<25 <sup>a</sup>	1.1(0.6-1.9)	1.3 (0.8-2.2)
25-29.9	1.1(0.4-5.4)	2.5 (1.3-4.4)
>=30 <sup>c</sup>	2.6 (1.2-5.6)	5.8 (3.5-9.5)
OR (a v c)	2.62 (0.89-7)	4.41 (2.05-9.44)

Significant increase in PR for coitus before the estimated day of ovulation vs outside fertile period OR 4.42 (2.33-8.2)  
 Unprotected intercourse also increased PR OR 4.64 (2.22-8.95)

## Advanced provision of levonorgestrel (Lo et al 2003)

1030 women using a less reliable method were randomised: (a) Treatment gp – 3 courses of LNG given (b) Control gp – educational pamphlet  
 FU 1 year and contacted every 3 months

No significant difference in regularity of use of contraception between the 2 groups; in both groups, regular contraceptive users rose from 60% pre-intervention to 65% post-intervention

Significantly more women in treatment group used EC (29.9% vs 22.9%); no. of EC courses used was also significantly higher in treatment group

## Pregnancies

	Clinic	Home
Pregnancies	9	8
EC not used	9	6
Reasons for not using EC		
Perceived low risk	4	4
Contraception fine	4	2
Cannot get EC	1	0

## Conclusion

- LNG more effective and better tolerated than Yuzpe regimen
- Mid-dose mifepristone probably more effective but not widely available
- LNG less effective in obese women, longer coitus-treatment interval and further acts of coitus in the same cycle after EC
- Early access to EC is important and women should be advised to abstain from further acts of unprotected intercourse after EC