DIAGNOSIS OF ECTOPIC PREGNANCY AFTER EMERGENCY CONTRACEPTION

- Dott.ssa Martina Bertin
EMERGENCY CONTRACEPTION: WHY?

Unplanned and undesired pregnancies constitute an important worldwide. It was estimated that 43.8 million induced abortions (i.e., 28 per 1000 women of reproductive age between 15 and 44) occurred globally in 2008, of which about 49% were unsafe. Li H-WR, et al., Emergency contraception, Best Practice & Research Clinical Obstetrics and Gynaecology (2014), http://dx.doi.org/10.1016/j.bpobgyn.2014.04.011.

The available evidence indicates that overall induced abortion rates are lower where abortion laws are liberal (12-19 per 1000 women of reproductive age); only in Eastern Europe and Eastern Asia, two subregions with a long history of reliance on abortion as a method for fertility regulation, are induced abortion rates higher.

Emergency contraception (EC), or post-coital contraception, refers to methods of contraception that can be used to prevent pregnancy in the few days after intercourse. It is intended for emergency use following unprotected intercourse, contraceptive failure or misuse (such as forgotten pills), rape or coerced sex.

The possible targets for postcoital contraception are:
- sperm transportation,
- follicular development,
- ovulation,
- fertilization,
- embryo development,
- endometrial receptivity,
- implantation
- corpus luteum.
EMERGENCY CONTRACEPTION: WHEN?

“(....) all conceptions resulted from intercourse that occurred during a six-day interval ending on the day of ovulation.”

- Almost 70% of all women requesting EC were aged **between 18 and 25 years**. Some 80% of all women were in a stable relationship with their partner, with fewer than 20% having had an occasional intercourse (..)

- Concerning the reasons for requesting EC, **condom breakage or slipping** was the most frequently cited (64%), followed by totally unprotected intercourse (28%), failed withdrawal (5%) and forgetting one or more pill (only 1.1%).

- More than one-third of the women interviewed had previously used an emergency contraceptive modality; although no one did so more than four times.

EMERGENCY CONTRACEPTION

There are two methods of emergency contraception:
1) emergency contraception pills (ECPs)
2) copper-bearing intrauterine devices (IUDs).

WHO recommends **levonorgestrel** for emergency contraceptive pill use. Ideally, this progestogen-only method should be taken as a single dose (1.5 mg) within five days of unprotected intercourse.

WHO recommends that a **copper-bearing IUD**, as an emergency contraceptive, be inserted within five days of unprotected intercourse. This may be an ideal emergency contraceptive for a woman who is hoping for an ongoing, highly effective contraceptive method.

http://www.who.int/mediacentre/factsheets/fs244/en/
## EMERGENCY CONTRACEPTION

### Table 1 Methods of emergency contraception in the UK

<table>
<thead>
<tr>
<th>Method</th>
<th>Class</th>
<th>Products</th>
<th>Recommended dose/use</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-bearing intrauterine device (Cu-IUD)</td>
<td>Intrauterine contraceptive method</td>
<td>Various types licensed for contraception</td>
<td>IUD retained until pregnancy excluded (e.g. onset of period) or for licensed duration of IUD (5–10 years)</td>
<td>Within the first 5 days (120 hours) following first UPSI in a cycle or within 5 days from the earliest estimated date of ovulation</td>
</tr>
<tr>
<td>Levonorgestrel (LNG)</td>
<td>Progestogen hormone</td>
<td>Levonelle One Step® (P)</td>
<td>1.5 mg single oral dose</td>
<td>Licensed for use within 72 hours of UPSI or contraceptive failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levonelle 1500® (POM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulipristal acetate (UPA)</td>
<td>Progesterone receptor modulator</td>
<td>ellaOne® (POM)</td>
<td>30 mg single oral dose</td>
<td>Licensed for use within 120 hours of UPSI or contraceptive failure</td>
</tr>
</tbody>
</table>

EC, emergency contraception; P, pharmacy medicine; POM, prescription-only medicine; UPSI, unprotected sexual intercourse.
Although the Centers for Disease Control and Prevention (CDC) and the World Health Organization's (WHO) Medical Eligibility Criteria for Contraceptive Use applies contraindications to daily use of hormonal contraceptives in some women based on their medical history, these contraindications do not apply to women seeking emergency contraception. ..

...In particular, cardiovascular disease, thrombophilic disorders, migraine, liver disease, and breastfeeding are considered conditions where the advantages of using the method generally outweigh the theoretical or proven risks...

LNG emergency contraception may be less effective or not effective in overweight and obese women. Product labeling for LNG EC is being updated with clinical trial information suggesting the contraceptive may be less effective in women 75 to 80 kg and not effective in women >80 kg and 80 kg correlates with BMI of about 30 kg/m² [obese category].

Overweight and obese women should be counseled about potentially reduced or absent efficacy of levonorgestrel emergency contraception as BMI increases above the normal range or at weights ≥75 kg, and they should be offered a copper-releasing IUD as first-line therapy to prevent pregnancy.

ULIPRISTAL EC

Ulipristal acetate is a selective progesterone receptor modulator with antagonistic and partial agonistic effects (a progesterone agonist/antagonist) at the progesterone receptor, thereby preventing the binding of progesterone. Ulipristal is a single pill containing 30 mg of ulipristal acetate and is indicated up to 120 hours after unprotected intercourse.

Unlike with hormonal emergency contraception, existing pregnancy must be excluded before prescribing ulipristal because of the risk of fetal loss if used in the first trimester of pregnancy.

Table 3: Summary of Clinical Trial Results for Women Who Received a Single Dose of ella (30 mg Ulipristal Acetate)

<table>
<thead>
<tr>
<th></th>
<th>Open-Label Study 48 to 120 Hours *</th>
<th>Single-Blind Comparative Study 0 to 72 Hours *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expected Pregnancy Rate</strong></td>
<td>N = 1,242</td>
<td>N = 844</td>
</tr>
<tr>
<td>Observed Pregnancy Rate **</td>
<td>5.5</td>
<td>5.6</td>
</tr>
<tr>
<td>(95% confidence interval)</td>
<td>2.2 (1.5, 3.2)</td>
<td>1.9 (1.1, 3.1)</td>
</tr>
</tbody>
</table>

* Time after unprotected intercourse when ella was taken
** Number of pregnancies per 100 women at risk for pregnancy

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf
Nowadays which emergency contraception? Comparison between past and present: latest news in terms of clinical efficacy, side effects and contraindications

Salvatore Gizzo MD¹, Tiziana Fanelli MD¹, Stefania Di Gangi MD¹, Carlo Saccardi MD,PhD¹², Tito Silvio Patrelli MD,PhD¹, Alessandra Zambon MD¹, Anis Omar MD¹, Donato D’Antona MD¹ & Giovanni Battista Nardelli MD¹

Ulipristal Acetate: Critical Review About Endometrial and Ovulatory Effects in Emergency Contraception

Bruno Mozzanega, MD¹, Salvatore Gizzo, MD¹, Stefania Di Gangi, MD¹, Erich Cosmi, MD¹, and Giovanni Battista Nardelli, MD¹

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf
ULIPRISTAL EC

There have also been preliminary in vitro data indicating that UPA at pharmacological concentrations could inhibit human sperm hyperactivation, as well as ciliary beating and muscular contraction in the human fallopian tube.


“...UPA effectiveness does not decrease depending on which of the 5 days it is taken after unprotected intercourse...This appears surprising if we assume that UPA effectiveness is due to an anti-ovulatory action which decreases as LH levels approach to peak...This suggests that the effectiveness of UPA relies on its endometrial effect. The inhibitory effect of UPA acts directly on the endometrial tissue through its inactivation of progesterone receptors. Thus, evidence shows that UPA endometrial effects can interfere with embryo implantation”

The precise mode of action of levonorgestrel (LNG) is incompletely understood but it is thought to work primarily by **inhibition of ovulation**. Administration of LNG appears to **prevent follicular rupture**. LNG taken prior to the luteinising hormone surge has been shown to result in ovulatory dysfunction in the subsequent 5 days, by which time any sperm in the reproductive tract will have become non-viable.

*FSRH Clinical Effectiveness Unit Guidance (August 2011) Emergency Contraception*

It works by delaying or inhibiting ovulation via the same mechanism (**negative feedback inhibition of gonadotropin secretion**) as conventional hormonal contraception. In a study in which LH levels were measured (as a marker for ovulation), it was found that LNG EC only worked when taken before the LH surge.
Deleterious effects of LNG impairing endometrial receptivity to subsequent implantation have not been found either in vivo or in vitro. LNG caused minimal changes in transcripts levels and, considering their nature and magnitude, it is unlikely that they would interfere with endometrial receptivity.


Following the repeated oral treatment, the immunoreactivity of both progesterone receptor (PR)-A and PR-B declined in glandular epithelium (P = 0.03 and P = 0.02, respectively) (…) However, levonorgestrel did not cause any significant endometrial changes.

Progesterone has been shown to regulate tubal transport of the zygote in vitro. Both muscular contractions and cilia activity are involved in the transportation. Cilia from the human fallopian tube beat significantly slower after treatment with high doses of progesterone, an effect that could be reversed by mifepristone.


Treatment with LNG (1.5 mg) on day LH peak + 2 did not affect the distribution of progesterone or estrogen receptors in the human fallopian tube in vivo.

Serum peak levels of LNG following the administration of 1.5-mg LNG are relatively high (35–40 nmol/L).

An in vitro study describes that high dose of LNG (≥20 nmol/L) significantly decreases tubal motility.

Pharmacokinetics of LNG shows that the serum level of hormone is above this threshold from 1 to 6 h after the intake of 1.5-mg LNG. Moreover, it is of paramount importance that the tubal musculature is exposed to LNG only for some minutes in a laboratory study, whereas its action lasts more than 5 days in vivo.

Devoto L et al. Pharmacokinetics and endometrial tissue levels of levonorgestrel after administration of a single 1.5-mg dose by the oral and vaginal route. Fertil Steril 2005;84:46–51.
LNG EC SPERM EFFECTS

In vitro data indicate that LNG in doses relevant for EC has no direct effect on sperm function.


LNG in a similar dose to that observed in serum following oral intake for EC had no effect on the number of motile spermatozoa recovered from the human fallopian tubes in vitro, their adhesion to the tubal epithelium, distribution or acrosome reaction rate.


LNG did not impair the cervical mucus either because viable spermatozoa were found in the genital tract 36–60 h after coitus and 24–48 h after LNG intake.

LNG EC and PREGNANCY RATE

The risk of pregnancy with LNG was 4.12%. A single dose of 1.5 mg LNG could reduce the pregnancy rate to 0.7%.


The ratio observed/expected pregnancies is an accepted means to define the efficacy of LNG-EC. The efficacy when used before ovulation was 100%. On the contrary, when used after ovulation has occurred, the number of observed and expected pregnancies is not statistically different, indicating that no reproductive process subsequent to ovulation is interfered with by LNG-EC.

Data from 136 studies on LNG revealed that 3 of 307 (1%) were ectopic, a rate which does not exceed the rate in the general population.

*K. Cleland et al. Ectopic pregnancy and emergency contraceptive pills: a systematic review*  
*Obstet Gynecol, 115 (2010), pp. 1263–1266*

In this review **five cases of ectopic pregnancy** were reported among 45,842 women and it did not look as if ectopic pregnancy was as common as seen in previous studies.


In women treated with LNG-EC, the rate of ectopic pregnancy does not exceed the rate observed in the general population, suggesting that embryo transport is not delayed by this treatment.
CASE REPORT

• V.A. 19 years old, italian white women

• P0 G0

• FAMILY HISTORY: ndp

• MEDICAL HISTORY: no previous surgery, no pathologies, no current therapy, never used E/P, no smoke, already taken EC without problem, Leiden Factor V heterozigosis.

LMP 24/02/2014 (regular menstruations)

On evening of 07/03/2014 she had an unprotected sexual intercourse (UPSI) (day 12 of the menstrual cycle). ..Patient came to Padua ER the morning after it for prescription of EC.
## CASE REPORT

<table>
<thead>
<tr>
<th>CASE REPORT</th>
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</thead>
</table>

**REGIONE VENETO**

**AZIENDA OSPEDALIERA DI PADOVA**

**SERVIZIO DI PRONTO SOCORSO E ACCETTAZIONE**

Responsabile Dott. Franco Tosato

**VERBALE DI PRONTO SOCORRO**

<table>
<thead>
<tr>
<th>Cartella DEA 2014 / 14913, 08/03/2014 09:49</th>
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</thead>
<tbody>
<tr>
<td>Assistente</td>
</tr>
<tr>
<td>Sesso</td>
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<tr>
<td>a DOLO</td>
</tr>
<tr>
<td>F.to</td>
</tr>
<tr>
<td>Residenza</td>
</tr>
<tr>
<td>Via</td>
</tr>
<tr>
<td>Codice Triage di ingresso:</td>
</tr>
<tr>
<td>Motivo di ingresso:</td>
</tr>
<tr>
<td>Modalità di arrivo:</td>
</tr>
<tr>
<td>Provenienza:</td>
</tr>
<tr>
<td>Operatore al triage:</td>
</tr>
</tbody>
</table>

**APERTURA - 08/03/2014 ore 10:56**

Dr. CASTIGLIONE GIULIA dal 08/03/2014 10:57


08/03/2014 10:58 VISITA MEDICA DI PRONTO SOCORRO

**CHIUSURA - 08/03/2014 ore 11:14**

Esito: DIMISSione

Diagnosi: CONTRACEZIONE D’EMERGENZA IN PAZ CON ETEROZIGOSI PER FATTORE V DI LEIDEN

Nota: SI PRESCRIVONO CALZE ELASTOCOMPRESSIVE PER PROFILASSI ANTITROMBOTICA PER ALMENO UN PAIO DI SETTIMANE. SI PRESCRIRE NO IRITRATTO URETRALE TORNÀ IN PS SE GONFIORRE AD UN ARTO O MANCANDO DI RESPIRO. Il/la paziente dichiara di essere informato/a sui pericoli, potenzialmente letali, cui si espone la decisione di assumere tale farmaco. Firma del paziente [Redacted] Al momento della firma il/la paziente risultà in grado di intendere e volere e di assumere decisione consapevole. Firma del Medico [Redacted]
CASE REPORT

EC has been correctly assumed, without episodes of vomiting or diarrhea.

Persistent spotting the days following EC assumption.
….but she did not ask for a ob/gyn consultation…

…after three week she was assuming AB for temperature and cold.. she complained of suddenly **right groin pain radiating to the right leg** so she went to Padua ER..

No risk factors for ectopic pregnancy were identified (no history of salpingitis, previous tubal surgery, previous ectopic pregnancy or intrauterine device use).
...Urine pregnancy test positive!!
Blood test at admission to ER

Plasmatic bHCG was 1021 U/L at access to Ob/Gyn Unit
Surgery: laparoscopic right salpingectomy (minimum hemoperitoneum)
### CASE REPORT

Blood test at day 1 after salpingectomy
CASE REPORT

DESCRIZIONE MACROSCOPICA

Repetto macroscopico (campione pervenuto fissato in formolina) [IRC]:
Salpinge della lunghezza di cm 15, con lume ectatico e a contenuto emorragico.
Il materiale inviato si processa in foto per esame istologico (1-9).
Informazioni cliniche (come segnalate in richiesta):
- Salpingectomia destra per gravidanza extraterina, 6° S.G. + 4 gg. PARA 0000.

DIAGNOSI

Salpinge con ectasia del lume in rapporto ad impianto gravidico con cellule del trofoblasto e villi coriali e con angiastasi e diffuso infarcimento emorragico della parete (1-9).
CASE REPORT

- Patient was well, no fever or vaginal bleeding was remarked and she was discharged on third day after salpingectomy.

- She continued AB for 7 days at home.

- bHCG dosage was repeated at 7 and 24 days after surgery and both them were under 20 U/L.
ECTOPIC PREGNANCY

Clinical manifestations typically appear six to eight weeks after the last normal menstrual period, but can occur later. Normal pregnancy discomforts (eg, breast tenderness, frequent urination, nausea) are often present in addition to the symptoms described below:

- Abdominal pain
- Amenorrhea
- Vaginal bleeding

These symptoms can occur in both ruptured and unruptured cases.

Ectopic pregnancy should be suspected in any women of reproductive age with these symptoms, especially those who have risk factors for an extrauterine pregnancy. However, they are the same as those associated with threatened abortion, which is far more common.

### ECTOPIC PREGNANCY

#### Risk factors for ectopic pregnancy

<table>
<thead>
<tr>
<th>Degree of risk</th>
<th>Risk factors</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Previous ectopic pregnancy</td>
<td>9.3-47</td>
</tr>
<tr>
<td></td>
<td>Previous tubal surgery</td>
<td>6.0-11.5</td>
</tr>
<tr>
<td></td>
<td>Tubal ligation</td>
<td>3.0-139</td>
</tr>
<tr>
<td></td>
<td>Tubal pathology</td>
<td>3.5-25</td>
</tr>
<tr>
<td></td>
<td>In utero DES exposure</td>
<td>2.4-13</td>
</tr>
<tr>
<td></td>
<td>Current IUD use</td>
<td>1.1-45</td>
</tr>
<tr>
<td>Moderate</td>
<td>Infertility</td>
<td>1.1-28</td>
</tr>
<tr>
<td></td>
<td>Previous cervicitis (gonorrhea, chlamydia)</td>
<td>2.8-3.7</td>
</tr>
<tr>
<td></td>
<td>History of pelvic inflammatory disease</td>
<td>2.1-3.0</td>
</tr>
<tr>
<td></td>
<td>Multiple sexual partners</td>
<td>1.4-4.8</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>2.3-3.9</td>
</tr>
<tr>
<td>Low</td>
<td>Previous pelvic/abdominal surgery</td>
<td>0.93-3.8</td>
</tr>
<tr>
<td></td>
<td>Vaginal douching</td>
<td>1.1-3.1</td>
</tr>
<tr>
<td></td>
<td>Early age of intercourse (&lt;18 years)</td>
<td>1.1-2.5</td>
</tr>
</tbody>
</table>
ECTOPIC PREGNANCY

The most common extra-uterine location is the fallopian tube (98 percent of all ectopic gestations). The prevalence of ectopic pregnancy among women who go to an emergency department with first trimester bleeding, pain, or both ranges from 6 to 16 percent.

The overall incidence of ectopic pregnancy increased during the mid twentieth century, approximately almost 20 per 1000 pregnancies.

This rising incidence is strongly associated with an increased incidence of pelvic inflammatory disease

ECTOPIC PREGNANCY

The differential diagnosis of lower abdominal pain in women includes urinary tract infection, kidney stones, diverticulitis, appendicitis, ovarian neoplasms, endometriosis, endometritis, leiomyomas, pelvic inflammatory disease, and pregnancy-related conditions.

Vaginal bleeding also has several pregnancy-related and nonpregnancy-related etiologies.

A pregnancy test is important in premenopausal women who present with abdominal pain or vaginal bleeding in order to guide the direction of further evaluation.

This combination of TVUS and hCG will permit a definitive diagnosis in almost all cases at a very early stage of pregnancy.

ECTOPIC PREGNANCY

The **discriminatory zone** is based upon the correlation between visibility of the gestational sac and the hCG concentration. It is defined as the serum hCG level above which a gestational sac should be visualized by ultrasound examination if an intrauterine pregnancy is present. In most institutions, this serum hCG level is **1500 or 2000 IU/L with TVUS** (the level is higher [6500 IU/L] with TA ultrasound). However, a single serum hCG measurement does **not** usually distinguish between ectopic and intrauterine pregnancy so that it is mandatory to repeat the dosage of hCG.


In one representative study, 185 of 188 (98 percent) intrauterine pregnancies in women with hCG above 1500 IU/L were visualized.

Randomised, double-blind trial in 10 countries.

4136 healthy women with regular menstrual cycles, who requested EC within 120 h of one unprotected coitus, to one of three regimens: 10 mg single dose mifepristone; 1·5 mg single-dose levonorgestrel; or two doses of 0·75 mg levonorgestrel given 12 h apart.

Of 4071 women with known outcome, pregnancy rates were:

-1·5 % (21/1359) in those given mifepristone,
-1·5 % (20/1356) in those assigned single-dose levonorgestrel,
-1·8% (24/1356) in women assigned two-dose levonorgestrel.

The RR of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0·83 (95% CI 0·46–1·50), and that for levonorgestrel (the two regimens combined) compared with mifepristone, 1·05 (0·63–1·76). Mifepristone and levonorgestrel do not differ in efficacy. A 1·5 mg single levonorgestrel dose can substitute two 0·75 mg doses 12 h apart.

LITERATURE CASE REPORT 1

A 27-year-old white woman, G1, PARA 0, presented at our clinic because of lower abdominal pain and prolonged vaginal bleeding during the previous 4 weeks.

No risk factors for ectopic pregnancy were identified (no history of salpingitis, previous tubal surgery, previous ectopic pregnancy or intrauterine device use, and Chlamydia trachomatis DNA screening proved negative). She had regular menstruations. She had an unprotected intercourse 6 weeks before the consultation (day 13 of the menstrual cycle). She took 1.5-mg LNG (Norlevo®) 5 h after this unplanned interaction. She reported no vomiting or irregular spotting after the ingestion of the medication but noted mild abdominal pain. On day 28 of the same menstrual cycle, she experienced light vaginal bleeding, which she interpreted as menstrual bleeding.

Transvaginal ultrasound revealed a complex hypoechogenic tubal mass sized 3.5×2.7 cm and pelvic fluid suspected to be blood were demonstrated. The serum β-human chorionic gonadotrophin level was 3927 IU/L.

25-year-old nulliparous woman with acute onset of pain in her lower abdomen. A urine pregnancy test was positive.

Her menstrual cycle was every 30 days, and her last menstrual period was 6 weeks prior to presentation. She had light vaginal bleeding 2 weeks earlier, which was interpreted by her as menses, following which spotting persisted. She did give a history of a ruptured condom approximately 10 days after her last normal period and took two doses of 750 mcg of LNG, 12 h apart. There was no history of repeat unprotected intercourse, and no risk factors for ectopic pregnancy were identified.

A transvaginal sonogram revealed no gestational sac in the endometrial cavity, with no adnexal mass and minimal free fluid in the pelvis. Serum beta-human chorionic gonadotrophin ($\beta$-hCG) was 3816.8 mIU/mL.

The patient was a 24-year-old unmarried female, G1 P0, and a normal menstrual period of 28 days. After a single unprotected intercourse in her follicular phase (day 11), she had taken 750 µg levonorgesterol (Norlevo™) 16 hour and 28 hours later.

Three weeks later, on the 15th of May, 2009, she was first seen in our hospital. Her complaints were lower abdominal pain and light vaginal bleeding.

The patient’s level of serum β-human chorionic gonadotropin (β-hCG) was 2980 mIU/ml. Transvaginal ultrasound showed a complex structure of 3x3x4.3 cm in diameter in her left tube, with no evidence of intrauterine pregnancy. A diagnosis of ectopic pregnancy was made.