Current Controversies with Emergency contraception

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Controversies

• Mechanism of action
• Repeat use
• Safety pregnancy
• Obesity
• Quick-start contraception
Mechanism of action

- LNG: Delay ovulation
- No significant effect on histology or molecular endometrium
- No effect on blastocyst implantation in vitro

Lalitkumar et al 2007
Gemzell Danielsson et al 2014
Ovulation Delay

*Brache et al Hum Reprod 2010*
- Single dose UPA 30mg (n=35)
- Immediate pre-ovulatory follicle 18mm
- UPA no ovulation at 5 days in 59%

*Croxatto et al Contraception 2004*
- LNG no ovulation 5 days 12% vs. placebo 13%

*Brache et al Contra 2013*
- After onset of LH surge still able delay ovulation
- 79% UPA, LNG 14%, placebo 10%
Mechanism of action UPA

- Post ovulatory EC dose
- Reduce endometrial thickness (normal range)
- No delay secretory development (histology)
  *Stratton et al Fertil Steril 2010*

- No effect UPA on implantation of blastocyst & endometrium *in vitro* model
  *Berger et al Hum Repro 2015*

Suggests UPA EC may not exert significant endometrial effect
Repeat UPA same cycle

- Study HRA2914-54 (EMA: unpublished) N=23
- UPA every 5/7 or 7/7 for 8 wks
- Ovulation delayed
- Most eventually ovulated (normal endo & mucus)
- Expected side effects inc. unscheduled bleed

- European Medicines Authority (EMA) Dec 2014: ‘repeated administration in same cycle is safe’
Safety : UPA & Pregnancy

- UPA still not widely used so data scarce
- Failure (pregnancy) is rare <2%
- Most women choose not to continue pregnancy
- Reporting is rare unless complications

- > 1 million use UPA (trials and post marketing)
- 376 pregnancies, outcome 232 (62%)
- 66% TOP
- 14% miscarriage (vs. 20% gen pop)
- Few ectopic (n=4)
- 27 pregnancies childbirth (28 babies)

*Levy et al Contra 2014*
UPA & pregnancy

• Optic nerve atrophy not thought to be causal

• Trisomy 21 (42 yr mother) exposure to UPA was at 6+ wks amenorrhea

• Fetal cardiac defect discovered at 12 weeks gestation - abortion performed at 13 weeks

• (1 woman exposed to UPA 10 mg for 10 days - healthy twins were delivered)

  Incidence of fetal anomaly below average rate
Risk of pregnancy obesity vs normal BMI group

Meta-analysis RCT’s UPA vs. LNG (n=3445)

<table>
<thead>
<tr>
<th>BMI group</th>
<th>LNG OR (95% CI)</th>
<th>UPA OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese v.s normal</td>
<td>4.41 (2.05-9.44) *</td>
<td>2.62 (0.89-7.00)</td>
</tr>
</tbody>
</table>

Limit of efficacy
LNG 26 Kg/m² (weight 70kg)
UPA 35 Kg/m² (weight 88kg)

* P=0.0002

Glasier, Cameron et al, Contra 2011
Obesity and EC effectiveness

• Secondary analysis, Ht & wt self-reported
• Numbers of obese participants
• Other LNG studies not observed BMI effect
• Some pharmacokinetic data LNG to support

Edelman et al Contra 2013

• EMA 2014: *Data not sufficiently robust to conclude with certainty that contraceptive effect reduced with BMI*

• *Women with obesity can use either LNG or UPA*

Ongoing pharmacokinetic studies UPA obese
Quick-start contraception after UPA?

‘Quick-start’ COC
• LNG & 7 days COC

• UPA & 14 days COC

• 7 days to ‘clear’ UPA + 7 quiescence = 14
• Based on theory

FSRH 2010 EC guidelines
UPA quick start COC study

- RCT (N=76)
- 18-35 yrs, BMI < 30 kg/m²
- Dominant follicle > 13 mm
- Randomise UPA or placebo
- Next day COC (microgynon®) for 21/7
- Visit every 2-3 days

TVU & blood (estradiol, prog)

*Cameron et al Hum Reprod 2015*
Results

- 62% Quiescence: med day 5 UPA, 6 Placebo
- 33% Ovulation: most < day 7, all by day 11
- No difference UPA vs Placebo
- Cannot say ‘when’ ovulation occurred

UPA does not affect COC
Cannot answer if COC affects UPA
UPA quick start POP study

Placebo controlled partial crossover (N=49)

• Midycle (follicle ≥ 14 mm) randomisation groups:
  – UPA & POP (DSG 75mcg for 20 days)
  – UPA & Placebo
  – Placebo & POP (DSG 75mcg for 20 days)

• Daily TVU until rupture, Cx mucus

UPA no effect on contraceptive action DSG
  (ovulation inhibition or cervical mucus)

Brache et al Hum Reprod 2015
Quick-start POP affects UPA

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<tr>
<th></th>
<th>Ovulation ≤ 5days</th>
<th>Median day ovulation</th>
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</thead>
<tbody>
<tr>
<td>UPA &amp; POP (n=29)</td>
<td>N=13 (45%) *</td>
<td>4</td>
</tr>
<tr>
<td>UPA &amp; Placebo (n=29)</td>
<td>N=1 (3%) *</td>
<td>8</td>
</tr>
<tr>
<td>Placebo &amp; POP (n=29)</td>
<td>N=11 (38%)</td>
<td>3</td>
</tr>
</tbody>
</table>

* P=0.0054

POP (DSG) after UPA affects UPA delay ovulation
Delay hormonal contra for at least 5 days after UPA
# UPA & hormonal contraception

<table>
<thead>
<tr>
<th>UPA then wait at least 5 days</th>
<th>Method (start UPA+5)</th>
<th>Requirement for additional contraception</th>
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</thead>
<tbody>
<tr>
<td>UPA + 5</td>
<td>COC/ring/patch</td>
<td>7 days</td>
</tr>
<tr>
<td>UPA +5</td>
<td>POP</td>
<td>2 days</td>
</tr>
<tr>
<td>UPA +5</td>
<td>Implant/Injectable</td>
<td>7 days</td>
</tr>
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UPA = day 0

Sept 2015 FSRH CEU statement
Conclusion

• Oral EC (LNG and UPA):
• No significant endometrial effect
• No adverse effect on pregnancy
• Repeat use UPA safe
• Obesity maybe less effective?
• Wait at least 5 days after UPA before hormonal contraception
• Need a better oral EC