Practical aspects of studies in females –
Aspects related to indication, hormonal status, pregnancy and lactation

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Studies in females

WHY should women be included in trials?
Background clinical trials in women
  • Guidelines, regulations
  • General considerations for the inclusion of female subjects

Choice of female population / contraception:
  ▪ Not fertile
    • postmenopausal
    • sterilized
  ▪ Fertile, not pregnant:
    • using hormonal contraception
    • spontaneous menstrual cycle
    • breastfeeding (timing of research)
  ▪ Pre-fertile
  ▪ Pregnant women
WHY should women be included in trials?

Different PK due to differences in:
- enzymes and transporters,
- amount of fat and body water.
- organ weight, binding proteins,
- time of food passage …

Different PD:
- differences in hormonal status (menstrual cycle)
- more AEs (approx...1,5-1,7 times more than male)
- more ventricular arrythmia (Torsade de Pointes) …

For many drugs the target population is at least 50% female
8 of 10 medicines which were withdrawn from the market by the FDA between 1997 and 2000 had more side effects in women than in men
Side effects might be identified earlier in women!
Guidelines and regulations

- **USA 1993:**
  - NIH ‘Revitalization Act’
    - No money for NIH-studies without including adequate amount of female subjects
  - FDA ‘Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs’
    - Routine inclusion of female subjects in ALL stages of development; number of females included should represent the user population

- **USA 1998:**
  - IND and NDA
    - Rejection of approval without ‘gender‘-analysis of the data

- **Since 1990:**
  - ICH Process
November 2000:
Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Inclusion of female subjects in the early phases of clinical studies:

- women – not fertile (sterilized, postmenopausal):
  - inclusion without Reprotox data possible

- women – fertile:
  - With „safe“ contraception (named in guideline, Pearl Index<1)
    - USA: Inclusion without Reprotox data possible
    - EU: Reprotox data should be available
    - Japan: Reprotox data must be available

- women without „safe“ contraception:
  - Reprotox data must be available
FDA and other public instances

Office of Women’s Health (OWH) established 1994 at the FDA
Under the Food and Drug Administration Modernization Act of 1997 (FDAMA) Sec. 115
Clinical Investigations. (b) Women and Minorities. -- Section 505(b)(1) 21 U.S.C.355(b)(1) was amended by adding at the end the following: “The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials . . . ”

To accomplish this task, CDER established an ad hoc working group, “FDAMA Women and Minorities Working Group” with representation from the Agency and the National Institutes of Health.

2010 Institute of Medicine (established under the Charter of the National Academy of Sciences), committee on women’s health research published: Women’s Health research, Progress, Pitfalls, and Promise
General considerations for the inclusion of women

- **Fertile women should not get pregnant when participating in a clinical trial,** independent of the phase of the trial, the fact if there is a Reprotox issue or Reprototox is known or unknown.

- **Women with the wish of pregnancy in the very near future should not participate** in a clinical trial (this should be evaluated beforehand)

- The safest population concerning avoidance of unwanted pregnancy are women without oocyte reserve – they might have disadvantages due to their higher incidence of morbidity caused by higher age

- Depending on the **choice and correct use** of contraception the risk of pregnancy is very different!

- **Contraception must** be mentioned in the written information of trials where fertile women are included

- **Use of “double Dutch”** (combination of “safe” contraception with male condom) minimizes the incidence of unwanted pregnancy!

- **In all female subjects in the fertile age regular pregnancy testing** should be included in the trial design
General considerations for the inclusion of women

- Subjects should be encouraged to report if a possible method failure might have occurred.
- There should be an informed gynaecologist who knows how to proceed in case of possible contraceptive method failure (use of “morning after pill”, insertion of an IUD or other).
- In case of possibly failed contraceptive method pregnancy tests should be performed weekly to be able to determine pregnancy as soon as possible.
- The principal investigator and the sponsor should feel responsible for choosing the “most suitable” contraception for the trial and involve the subjects to take responsibility.
- For Reprotox issues: Be aware that all premenopausal women with intact ovaries can get offspring from their own pool of oocytes! Even successful sterilization is not definite in the time of in vitro fertilization.
- For all trials where use of condoms is advised condoms should be provided to the subjects!
First choice: non-fertile women

- Postmenopausal (spontaneous *or ovarectomized)
  
  **Definition: after last menstrual bleeding** (defined after 1 year)
  
  - early phase: within the first 2 years
  - Lab: FSH > 25mIU/ml, Estradiol <35pg/ml
  - **late phase: after two years**
  - pool of functioning oocytes is empty (irreversible)
  - Lab: FSH > 50mIU/ml, Estradiol <35pg/ml

  **Advantage:** No risk for unintended pregnancy

  **Disadvantage:** higher risk of morbidity due to age

  **Possible menopause related symptoms (AEs):**
  
  - i.e. hot flushes, vaginal dryness, night sweats (insomnia), headache, migraine, mood changes (irritability, depression) - pronounced in early phase, painful joints, osteoporosis, urinary incontinence, weight changes, dry skin, eyes, mouth

  *The menopausal transition, Fertility and Sterility, Vol.90, Suppl.3 November 2008
## Pearl Index of different contraceptives

<table>
<thead>
<tr>
<th>Birth control method</th>
<th>Brand/common name</th>
<th>Typical-use failure rate (%)</th>
<th>Perfect-use failure rate (%)</th>
<th>Type</th>
<th>Implementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progestogen Implant</td>
<td>Implanon</td>
<td>0.05</td>
<td>0.05</td>
<td>Progestogen</td>
<td>Subdermal implant</td>
</tr>
<tr>
<td>IUD with progestogen</td>
<td>Mirena</td>
<td>0.2</td>
<td>0.2</td>
<td>Intrauterine &amp; progestogen</td>
<td>Intrauterine</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>&quot;female sterilization&quot;</td>
<td>0.5</td>
<td>0.5</td>
<td>Sterilization</td>
<td>Surgical procedure</td>
</tr>
<tr>
<td>IUD with copper</td>
<td>Multiload</td>
<td>0.8</td>
<td>0.6</td>
<td>Intrauterine &amp; copper</td>
<td>Intrauterine</td>
</tr>
<tr>
<td>Depot Progestogen</td>
<td>Depo Provera</td>
<td>3</td>
<td>0.3</td>
<td>Progestogen</td>
<td>Injection</td>
</tr>
<tr>
<td>Combined oral contraceptive pill</td>
<td>&quot;the Pill&quot;</td>
<td>8</td>
<td>0.3</td>
<td>Estrogen &amp; progestogen</td>
<td>Oral medication</td>
</tr>
<tr>
<td>Progestogen only pill</td>
<td>&quot;POP&quot;, &quot;minipill&quot;</td>
<td>8</td>
<td>0.3</td>
<td>Progestogen</td>
<td>Oral medication</td>
</tr>
<tr>
<td>Male latex condom</td>
<td>Condom</td>
<td>15</td>
<td>2</td>
<td>Barrier</td>
<td>Placed on erect penis</td>
</tr>
<tr>
<td>Coitus interruptus</td>
<td>&quot;withdrawal method&quot;</td>
<td>27</td>
<td>4</td>
<td>Behavioral</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>None</td>
<td>unprotected coitus</td>
<td>85</td>
<td>85</td>
<td>depending on age</td>
<td></td>
</tr>
</tbody>
</table>

*Data derived from Wikipedia*
Second choice: Hormonal fertile - Sterilized

- **Sterilized** (tubal ligation)

Incidence in Europe <3%, Asia 3-35%, USA ca. 20% decreasing

**Advantage:**
According to ICH guideline non-fertile (no Reprotox needed)
Very low chance of fertilization and pregnancy during trial
Pearl index in first year after tubal ligation 0,5%, later decreasing

**Disadvantage:**
Incidence in western countries decreasing!
Cycles are not synchronized, bleeding can occur at any time
Fertilization of oocyte is still possible (IVF)

**Possible spontaneous cycle related symptoms (AEs):**
  i.e. headache, migraine, mood changes (PMS, PMDD), lower abdominal pain
  (with ovulation), dysmenorrhea, weight changes
Third choice: Hormonal fertile – safe contraception

- **IUD** with progestogen or **progestogen implant**

  Incidence IUD in Europe 2-15%, Asia ??, USA <1% increasing

  Incidence Progestogen implant ??

  **Advantage:** Pearl index 0,2% or 0,05% (lower than tubal ligation in the first year)

  **Disadvantage:**
  
  Hormonal treatment (in case of possible interaction with hormones)

  Possibility of ectopic pregnancy IUD(very low)

  **Possible IUD related symptoms:**
  
  i.e. breast tenderness, nausea, functional ovarian cyst, amenorrhea,

  intramenstrual bleeding

  **Possible spontaneous cycle related symptoms (AEs):**

  i.e. headache, migraine, mood changes (PMS, PMDD), lower abdominal pain

  (with ovulation), dysmenorrhea, weight changes
Third choice: Hormonal fertile – safe contraception

• Combined (oral) Contraceptive „the pill“
  Incidence Europe 30-75%, Asia 2-30%, USA 17%

  Advantage:
  Pearl index 0,3%, even higher when used without or with shortened pill-free interval,
  Easy to manage, bleeding can be synchronized or avoided (use of 2 blisters without pill-free interval)

  Disadvantage:
  Intake should be monitored, „forgotten pill scenario“ has to be developed, possibility of consult of gynaecologist should exist.

  Possible C(O)C related symptoms:
  i.e. headache, migraine, mood changes (depression), abdominal pain, weight increase, breast tenderness, decrease of libido, very rarely thrombosis
Pearl index of different COCs

- Pearl index of COC **differs** between different progestogens => Choose COC which is most suitable in your country, taking into account the Pearl Index
- Pearl index **increases** with lowering of EE and progestin => Choose 30µg EE containing COC rather than 20µg EE containing COC
- Pearl index **decreases** with shortening of pill-free interval => Skip pill-free interval or start new blister after 4 days pill-free interval
- It is for most OC’s an “in label” treatment to skip 1 pill free interval => Check package insert of COC during planning of the trial
- Pearl index **increases** with forgotten pills, especially when forgotten near the pill-free interval => Monitor intake of COC of the subject (i.e. diary)
- In case of forgotten pills the investigator should know how to proceed Think of a “forgotten pill scenario” before starting the trial and inform the subjects adequately
- **Be aware that COC intake is important for the outcome of the trial**
Third choice: Hormonal fertile – safe contraception

- IUD (copper)
  Incidence in Europe 2-15%, Asia ca. 1-30%, USA 2% decreasing

**Advantage:**
- No hormonal treatment (in case of possible interaction with hormones)
  - Pearl index 0.6%

**Disadvantage:**
- Incidence decreasing
- Possibility of ectopic pregnancy

**Possible IUD related symptoms:**
- i.e. hypermenorrhea, anaemia, increased dysmenorrhea

**Possible spontaneous cycle related symptoms (AEs):**
- i.e. headache, migraine, mood changes (PMS, PMDD), lower abdominal pain (with ovulation), weight changes
Last choice: no „safe“ contraception

- Condom (female or male), spermicides, diaphragm etc. incidence in Europe, Asia and USA depending on the method

Advantage:
No hormonal treatment (in case of possible interaction with hormones)

Disadvantage:
Even with combined use risk of pregnancy higher than before mentioned methods; Specialist should be involved
TRY TO AVOID IT IF POSSIBLE!

Possible method related symptoms:
- depending on the method

Possible spontaneous cycle related symptoms (AEs):
- i.e. headache, migraine, mood changes (PMS, PMDD), lower abdominal pain (with ovulation), weight changes
Order of choice female subjects concerning risk of pregnancy

SUMMARY
1. Late postmenopausal
2. Sterilized
3. Subject compliance independent
   • Progestogen IUD or implant
   • (IUD)
Subject compliance dependent
• COC
1. Mechanical or other contraception

Other reasons can change order of the choice, i.e. availability, co-morbidity, target group of treatment, planning or recruitment issues
Breastfeeding women

- Trials examining PK of substances in breastmilk are possible!
  - This should be done *directly after cessation of breastfeeding* when the milk production is still ongoing
  - Breast pumps should be used after feeding of the child is stopped
  - Studies have to be organized flexible (kinetic sampling at home instead of in house)
  - Recruitment is not as difficult as expected

- **Trials where the breastfeeding continues should be avoided if PK data in breast milk are not available!**
CONCLUSION

(trials in) women are not so difficult...

don’t be scared
-be prepared!!