Herbal medicines in pregnancy – pharmacovigilance and risk communication

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PVZ Embryotox I

- Publicly funded institution since 1988
- Provides independent information to the safety and tolerance of drugs during pregnancy and lactation to healthcare professionals and pregnant women
- Individual consultations are available drawing on the results from the institute's own database and other working groups
- Multidisciplinary team, i.e. obstetrics/gynaecology, paediatrics, pharmacology, human genetics, internal medicine, anaesthesiology
PVZ Embryotox II

- Regularly updated information is also available via the open access database [www.embryotox.de](http://www.embryotox.de) covering 400 drugs
The aim is to provide a better evidence for medical safety through

- Identification of adverse drug reaction
- Transmission to responsible federal authorities
- Detection of signals
- Conducting cohort studies or case control studies

→ To prevent prenatal development disorders
→ To reduce unnecessary invasive diagnostic and terminations of wanted pregnancies due to overestimation of a risk of exposure to drugs
Embryotox: consultation combined with pregnancy outcome documentation

Embryotox data ascertainment from consultation to pregnancy follow-up

Week of gestation at request

Week of pregnancy

- 2014  - 2015  - 2016

EDOB, estimated date of birth
FUP, follow-up
HCP, health care professional
LMP, last menstrual period
Risk communication

1. **Recommendation** on drugs of choice for a particular disease

2. A woman has already taken a suspect drug during pregnancy (teratogen? Like MTX, thalidomide, valproate, tretinoin)

3. A baby is born with a birth defect suspected to be caused by a drug
### Causes of congenital malformations

**Mean risk for major malformation: 3-5%**

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>chromosomal</td>
<td>16 - 25</td>
</tr>
<tr>
<td>intrauterine factors</td>
<td>2</td>
</tr>
<tr>
<td>Medicinal drugs, drugs of abuse, environmental pollution, hyperthermia, radioactivity</td>
<td>2 - 4</td>
</tr>
<tr>
<td>Maternal diseases</td>
<td>2 - 4</td>
</tr>
<tr>
<td>unknown, multifactorial</td>
<td>ca. 60</td>
</tr>
</tbody>
</table>

Use of Herbal medicinal products (HMP) regarding ongoing pregnancies PVZ Embryotox

- 11,814 regarding an ongoing pregnancy (maternal exposure): 725 herbal medicines → 6%

- Most frequently used: Valerian, St. John's Wort, Ivy, Thyme, Ginger, Cranberry
Popularity of HMP in pregnancy

• In Nigeria, Fekeye et al. recovered 67.5% of herbal medicine use among pregnant women.

• German survey of 139 pregnant women, 96% took CAM (especially phytotherapeutics).

• The prevalence of HMP use during pregnancy in Middle East countries ranges between 22-75%.

• American study: 35.8% of 2673 women used also at least one form of CAM.

→ only 51.8% of these women had discussed it with their physician.

References:
Reasons for preference of HMP during pregnancy

- Natural = safe\(^1\)

- Desire for more „natural“ alternatives\(^2\)

- To treat illnesses but also to enhance nutrition, to stay healthy\(^3\)

- Studies\(^4,5\) have shown that HMP in pregnancy are most often used for
  - Nausea and Vomiting
  - Common Cold
  - Anxiety
  - Urinary tract problems
  - Constipation
  - Backpain
  - Induction/ease of labour

➢ advice from midwives or family and friends

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\(^1\) Adams C, Cannell S. Women’s beliefs about “natural” hormones and natural hormone replacement therapy. Menopause 2001;8:433–440

\(^2\) Kennedy et al. Safety classification of herbal medicines used in pregnancy in a multinational study 2016. BMC Complementary and Alternative Medicine 16:10


\(^4\) Ranzini, A. Allen, Y. Use of complementary medicines and therapies among obstetric patients Obstetrics & Gynecology, Suppl. 4 (2001), p. pS4

Objections concerning the use of HMP in pregnancy

- Little information about the possible risks in pregnancy
- Limited standards for the preparation/ amounts of specific ingredients in the products marketed\(^1\)
- May contain contaminants from the agricultural or manufacturing processes\(^2\)
- Certain herbs can affect the muscle tone of the uterus, abortifacients or teratogens\(^3\)

→ **natural ≠ safe**

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Studies on HMP during pregnancy

• 14 randomized controlled trials (RCT) related to herb efficacy in pregnancy
  → Evaluating 5 different herbal medicines (Ginger, Cranberry, St. John’s wort, Rasberry and Garlic)
  → With the exception of ginger, no data support the use of any herbal supplement during pregnancy

• 9 RCTs, very few or no additional side effects compared with placebo were observed for herbal remedies

• Norwegian study: 39 % used possibly harmful herbal medicinal products or herbs, where information about safety in pregnancy was missing

• Multinational cross-sectional study: Recommendation to take a contraindicated herbal medicine was 3 times more likely to be from a health care professional than an informal source

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**Ginger (Zingiber officinale)**

- Most widely used herbal therapy for Nausea and vomiting in pregnancy (NVP)\(^1\)

- NVP affects approximately 80–90% of pregnant women\(^2\)

- 3 placebo-controlled trials addressed the safety and efficacy for morning sickness\(^3,4,5\)
  - normal ranges of birth weight, gestational age, Apgar scores, and frequencies of congenital abnormalities compared to the general population
  - safe to use during pregnancy (up to 250 mg four times a day)

- Inhibition of thromboxane synthetase may affect testosterone binding in the fetus\(^6\)
  - Not recommended by the Committee on Herbal medicinal products\(^7\)

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\(^2\) Shawahna R, Taha A. Which potential harms and benefits of using ginger in the management of nausea and vomiting of pregnancy should be addressed? a consensual study among pregnant women and gynecologists. BMC Complementary and Alternative Medicine (2017) 17:204


\(^6\) Backon J. Ginger in preventing nausea and vomiting of pregnancy; a caveat due to its thromboxane synthetase activity and effect on testosterone binding. Eur J Obstet Gynecol Reprod Biol. 1991 Nov 26;42(2):163-4

\(^7\) Wiesner J, Knöss W. Herbal medicinal products in pregnancy - which data are available? Reprod Toxicol. 2017 Sep;72:142-152

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Conflicting recommendation
Cranberry (Vaccinium macrocarpon)

• Cranberry is frequently used for Urinary tract infections (UTI) prophylaxis and treatment

• UTIs are the most common type of infection during pregnancy, affecting up to 10% of pregnant women

• UTIs may lead to serious maternal and fetal complications (premature birth, intrauterine growth restriction, increased neonatal mortality and pre-eclampsia)

• Retrospective cohort study 68522 women, 919 used cranberry in pregnancy → no negative fetal or pregnancy outcome

• Randomised controlled study 188 pregnant women, 125 with daily Cranberry-Juice consumption → No negative effect on pregnancy outcome → Evidence to support its effectiveness in UTI treatment in pregnancy is weak

Temporary use of cranberry preparation in food amounts is acceptable
No use as alternative to conventional prescribed medication for UTI

2 Aktuelle Leitlinien HWI, AWMF online
Considerations for Pregnancy Part 1

- Is there evidence-based efficacy of the HMP?

- Does evidence-based information on the risk/safety in pregnancy exist?

- Is the drug licensed by the national drug authorities?

- What is the origin of the herbal preparation?

- Avoid alcoholic preparations!
Considerations for Pregnancy Part 2

• Is a uterine stimulating effect known?
  • Blue cohosh (Caulophyllum thalictroides), Black Cohosh (Cimicifuga racemosa),
  • Angelica root (Angelicae radix)
  • Senna, Aloe (Anthraquinone laxatives)
  • Lovage (Levisticum officinale)

• Is an estrogenic effect known?
  • Chaste tree (Vitex agnus-castus)

• Avoid plants with pyrrolizidine alkaloids (PA)¹
  • Coltsfood (Tussilago farfara)
  • Comfrey (Symphytum officinale)

• Consider potential interactions
  St John’s wort

Conclusion

• Very few/no side effects are generally observed for HMP

• Long traditional clinical use during pregnancy

• Some HMP can cause harm in pregnancy

• There are little randomized controlled studies of safety or teratogenicity

• Use of HMP is prevalent among pregnant women worldwide

• More high quality research is needed
Thank you for your attention!
Embryotox: consultations 1997-2016

Beratungszahlen 1997 bis 2016

- Maternal
- Paternal
- Stillanfragen
Embryotox: consultations for
Percentage of herbal medicines used and the number of women who used these herbal medicines by safety classification, overall and by region

<table>
<thead>
<tr>
<th>Region</th>
<th>Herbals used (n=126)</th>
<th>Women used (n=2,379)</th>
<th>Herbals used (n=89)</th>
<th>Women used (n=768)</th>
<th>Herbals used (n=53)</th>
<th>Women used (n=274)</th>
<th>Herbals used (n=83)</th>
<th>Women used (n=1,119)</th>
<th>Herbals used (n=41)</th>
<th>Women used (n=129)</th>
<th>Herbals used (n=23)</th>
<th>Women used (n=89)</th>
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<td>21.4</td>
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<tr>
<td>Western Europe</td>
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<tr>
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Valerian (Valeriana officinalis)

- Valerian is recognized for its sedative and soothing medicinal properties and is frequently used to ease symptoms of insomnia\(^1\)
- Approximately 78-80% of pregnant women experience sleep disturbances\(^2\)
- Long traditional clinical use
- Surveys\(^3,4\) in 2008-2013 indicated that valerian was one of the most commonly used herbal products during pregnancy
- Norwegian study\(^3\): data from Swedish Medical Birth Register, 98 pregnant women used valerian preparation (86 preparation with single ingredient)
  → No unfavourable effect on pregnancy outcome
- Hungarian study\(^4\): 2 cases after suicide dosage in early pregnancy
  → Children without congenital abnormalities or long-term damage

occasional use is safe, no alcoholic preparations!

\(^2\) Hung HM, Chiang HC Non-Pharmacological Interventions for Pregnancy-Related Sleep Disturbances. Hu Li Za Zhi 2017 Feb;64(1):112-119