The FETAL TOBACCO SYNDROME

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• Fetal Tobacco Syndrome - A statement of the Austrian Societies for General- and Family Medicine (ÖGAM)
Gynecology and Obstetrics (ÖGGG)
Hygiene, Microbiology and Preventive Medicine (ÖGHMP)
Pediatrics and Adolescence Medicine (ÖGKJ)
Pneumology (ÖGP)

• Not only active smoking can harm the fetus, also ETS

• 1986 “first description” of the fetal tobacco syndrome¹

• Smoking of ≥ 5 cig/d during pregnancy and symmetric growth retardation without other detectable cause

• ~ 10,000 publications to date on the detrimental effects of tobacco in pregnancy on the fetus

1) Nieburg et al. Fetal tobacco syndrome JAMA 1986 15;256(7):862-863
• Mechanism: Pathophysiology
• Recent scientific findings of health effects
• Possibilities for smoking cessation in pregnancy
Epidemiology

• 15-25% of all pregnant women smoke\(^1\)
• Overall decreasing trend in prevalence\(^2\)
• Woman <20 a: increase in prevalence

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1) Cnatteringius S et al. Nicotine & Tobacco Research 2004
**Fetoplacental Unit**

- morphological changes in the placenta are seen in the 1\textsuperscript{st} Trimenon
- direct damage of Cytotrophoblast proliferation and differentiation\textsuperscript{1}
- Thickening of the basement membrane of the Trophoblast
- Collagen increase in villous mesenchyme & decreased vascularisation\textsuperscript{2}

3) Zdravkovic et al. Placenta 2005
Fetoplacental Unit

NICOTINE:

• AA uptake decreased
• Bindes to nicotinic Acetylcholin-Receptors (nACH = Signal for AA uptake, blood flow and vascularisation)\(^1\), chronic stimulation might cause unbalanced activation or functional desensitisation

CADMIUM:

• Quick uptake through placenta\(^2\)
• Accumulation in placenta
• 11 beta HSD2 expression reduced in Cadmium-exposed cells → potential effect on fetal growth\(^3\)

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1) Jauniaux et al. Early Human Dev. 2007
2) Salpietro J.Perinatal Medicine 2002
3) Yang et al. Am J Physiol Endocrinol Metab 2006
Fetoplacental Unit

Placenta:

- placental abruption: high evidence in many studies (OR 1.4-4.0)\(^1\)
- dose response relationship\(^2\)
- risk reduction by smoking cessation in early pregnancy\(^3\)

3) Naeye RL. Obstet Gynecol 1980

Castles et al 1999
Small for gestational age

- strong and direct association with smoking OR 1.5-2.9 \(^1\)
- birth weight reduced by approx. 10-12g per cigarettes/d \(^2\)
- effect doubles during the 3\(^{rd}\) Trimenon \(^2\)
- no increase of risk in woman with smoking cessation in 1\(^{st}\) Trimenon \(^3\)
- mothers with certain Genotypes especially at risk \(^4\)

1) Cnattingius S. Nicotine & Tobacco Research 2004
2) Bernstein et al. Obstet Gynecol. 2005
4) Wang et al. JAMA 2002
Fetal Mortality

• spontaneous abortion (OR 1.2-1.8)$^1$; some studies show no effect$^2$

• stillbirth (=fetal death ≥20GA): RR 1.2-1.8
  some find a dose response (1-9; >9 cig/d)$^4$

3) Cnattinguis S. Nicotine Tobac Res 2004
4) Högberg et al. BJOG 2007
Preterm Birth

• increase in risk for preterm birth: 1.2-1.6

Preterm Birth

• increase in risk for preterm birth: 1.2-1.6
  (vs. non smokers)\(^1\)

• stronger association with "very preterm" infants
  (<32.GA)\(^2\)

• association with premature rupture of the membranes
  (reason for preterm birth) 2.0-3.0\(^3\)

2) Cnattingius et al. NEJM 1999
Mortality in the First Year of Life

- SIDS: RR 2.0-3.0\(^1\), Metanalysis: very consistent results, dose response relationship \(^2\); 1/3 preventable separation of current ETS effect not possible in all studies

- Mortality before 1\(^{st}\) birthday increase by 4% for every 10 cig/d\(^3\)

Asthma and wheezing

Increased risk for asthma (OR 1.8 95% CI 1.1 to 2.9) and "wheezing".

Pattenden et al. Tob Control 2006
Orofacial Clefts

- consistant results in various studies\(^1\)
- Metaanalysis: RR 1.2-1.3\(^2\)
- dose-response 1-20, >20 cig. (OR 1.7)\(^3\)

\(^1\) Honein et al. Epidemiology 2007
\(^2\) Little et al. Cleft Palate Craniofac J 2004
\(^3\) Chung et al. Plast Reconstr Surg 1999
Congenital Malformations

Metaanalyses:
50 a
172 studies
173 687 cases
11 674 332 controls

Hackshaw et al. Hum Reprod Update 2011
### Congenital Malformations

**Metaanalyses:**

- **50 a**
- **172 studies**
- **173 687 cases**
- **11 674 332 controls**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. studies</th>
<th>Pooled OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>25 (29,288)</td>
<td>1.09 (1.02-1.17)</td>
</tr>
<tr>
<td>Limb reduction</td>
<td>19 (26,707)</td>
<td>1.09 (1.00-2.18)</td>
</tr>
<tr>
<td>Digit anomaly</td>
<td></td>
<td></td>
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<tr>
<td>Clubfoot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>5 (1131)</td>
<td>1.39 (1.09-1.79)</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td></td>
<td></td>
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<tr>
<td>Facial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral clefts</td>
<td>10 (5,076)</td>
<td>1.19 (1.06-1.35)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
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<tr>
<td>Gastrocystis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omphalocele</td>
<td>7 (546)</td>
<td>1.19 (0.95-1.48)</td>
</tr>
<tr>
<td>Anal atresia</td>
<td>7 (1679)</td>
<td>1.20 (1.06-1.36)</td>
</tr>
<tr>
<td>Hernia'</td>
<td>4 (941)</td>
<td>1.40 (1.23-1.59)</td>
</tr>
<tr>
<td>Oesophageal fistula</td>
<td>7 (1987)</td>
<td>0.93 (0.81-1.07)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any genital</td>
<td>40 (24,081)</td>
<td>1.05 (0.98-1.12)</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>32 (21,505)</td>
<td>1.01 (0.93-1.10)</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>18 (8753)</td>
<td>1.13 (1.02-1.25)</td>
</tr>
<tr>
<td>Renal/urinary tract</td>
<td>15 (12,047)</td>
<td>0.90 (0.85-0.95)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anencephaly/spina bifida</td>
<td>9 (3330)</td>
<td>1.15 (0.95-1.39)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
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<tr>
<td>All defects together</td>
<td>58 (67,718)</td>
<td>1.01 (0.96-1.07)</td>
</tr>
</tbody>
</table>

Note: Decreased risk in smokers vs. Increased risk in smokers

Odds ratio (95% CI)
Congenital Malformations

- anectotal evidence for CNS-malformations\(^1\)
- intra and periventricular hemorrhage \(^2\)
- neural tube defects \(^3\)

1. Lavezzi et al. 2005
2. Maturri et al. 2011
3. Suarez et al. 2008
Obesity

• Metaanalysis of 17 Publications\(^1\):
  signifikant association in children ≥3 a

• OR for BMI>95.Percentile: 1,6 (95%CI 1,4-1,9)

1) Ino T. Pediatr Int 2010
Psychosocial Pathologies

- Metaanalysis of 13 population based studies

- various different study designs:
  association OR 2.4 (95%CI 1.6-3.5) for ADHD

1) Langley et al. Minerva Pediatr 2005
Neurodevelopment

Prenatal tobacco and postnatal secondhand smoke exposure is consistently associated with problems in multiple domains of children’s neurodevelopment and behavior.

PTE affects speech processing, levels of irritability and hypertonicity, attention levels, ability to self-regulate, need to be handled, and response to novelty preference in infants

**Early childhood:** mostly behavioral outcomes including activity and inattention and externalizing behaviors, including conduct and antisocial behavior

**Adolescents:** PTE predicted increased ADHD, modulation of the cerebral cortex & white matter structure & nicotine addiction

1) Hermann et al. Curr Opin Ped 2008
2) Cornelius et al. Curr Opin Neurol 2009
Smoking cessation in pregnancy

- 20-40% stop smoking during pregnancy \(^1\)

- Success of interventions (Metaanalysis of 34 studies): 16% intervention, 9% controls\(^2\)

- high relapse-rate after pregnancy (up to 80\%)\(^3\)

2) Lumley et al. Cochrane Review 2009
3) Lawrence et al. J Health Psychol 2005
Smoking cessation in pregnancy

- Multi-Media campaign, Telephone Consulting, Financial Incentives, Biofeedback
  - relatively weak effects\(^1\)

- Probleme: Nicotine metabolism increased in pregnancy\(^2\)

- Motivation!

1) Schnoll et al. J Womens Health 2007
2) Dempsey et al. J Pharmacol Exp Ther 2002
Nicotine replacement

- patch, gum, Inhaler, nasal spray\(^1\)
- Metaanalysis: 5 Trails, insufficient evidence for success and safety \(^2\)

1) Hotham et al. Drug Alcohol Rev. 2002
1) Coleman et al. Addiction 2011
Medication

- Studies with antidepressants\(^1\), Bupropion\(^2\), MAO-Inhibitors\(^3\)

- Cochrane-Analysis\(^4\): selektive Serotonin Reuptake inhibitors (Fluoxetin) ineffektiv, Nortryptilin moderately effective, Bupropion most effective

- Safety of Bupropion: no teratogenicity;

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1) Haggstram 2006
2) Fossati 2007
3) Berlin 1995
4) Hughes et al. Cochrane database review 2007
Medication during pregnancy

• **Bromocriptin**: indirect evidence in study on subfertile women (n=4600)\(^1\):
  
  50 % less smokers in the Intervention group,
  
  Safety shown in ~2500 pregnancies prospectively

• **Varenicline**: Nicotine rec. Agonist: No studies in Pregnancy \(^2\)

• **Nicotine - Injection**: Antibody against Nicotine: no Phase III\(^3\)

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1) Murphy et al. Addict Biol 2002
2) Stack et al. Pharmacotherapy 2007
Take Home Message

- FTS results in increased Morbidity and Mortality in prenatal & postnatal life
- recommend earliest possible cessation
The Fetal Tobacco Syndrome

Damage of the Fetoplacental Unit

Infant Mortality

Lung function
  Asthma

Malformations

SIDS

obesity
  ADHS

Preterm birth

Learning difficulties

Placental complications

Fetal growth retardation

Asthma

obesity

ADHS

Learning difficulties