Practical aspects and feasibility of studies in females – aspects related to pregnancy

BACKGROUND

The use of drugs in pregnancy is not a rare event; international surveys have shown that up to 85% of pregnant women are exposed to an average of 2.5 medications during the gestational period (Int J Gynaecol Obstet 1992; 39: 185-196).

Part of these exposures (e.g. 50%) is unplanned because many women are not aware of their pregnancies, mainly during the first trimester.

Pregnant women are usually not included in pre-marketing drug investigations. Consequently most drugs cannot be labeled for use during pregnancy. SPC information is often not helpful for risk assessment.

However, pregnant women need and seek health information. The internet and mass media in general is fraught with inaccuracies and a lack of evidence-based information. These issues have led to the creation or development of what is today known as the Teratology Information Service (TIS).

TIS provide risk assessments of drug use in pregnancy (and during lactation). They belong to either the European Network of TIS (ENTIS) or the Organisation of TIS in the Americas (OTIS). These services also conduct follow-up studies (case-registry studies and prospective cohort-control studies) to learn about what occurred during the course of pregnancy and the health of the newborn.

Examples of Recent Multicentre Studies Conducted by TIS Collaborations

DRUGS	NUMBER OF TIS INVOLVED	LOCATIONS	TOTAL EXPOSED SUBJECTS	TOTAL CONTROLS	REFERENCE
Asthma medications	15	Canada, USA	654	303	Bakhireva et al.[17]
Dipyrone	4	Israel, Italy	108	108	Bar-Oz et al.[18]
Bupropion	2	Canada, USA	136	133	Chan et al.[19]
Haloperidol/Penfluridol	4	Germany, Israel, Italy, Netherlands	215	631	Diav-Citrin et al.[20]
Proton Pump Inhibitors	8	Finland, France, Germany, Greede, Israel, Italy, Netherlands	295	868	Diav-Citrin et al.[21]
H2-Blockers	18	Brazil, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Spain, Switzerland, UK	553	1390	Garbis et al.[22]
Permethrins	2	Australia, Canada	113	113	Kennedy et al.[23]
Amoxicillin/ Clavulinic Acid	2	Israel	191	191	Berkovitch et al.[24]
Loratadine	4	Brazil, Canada, Israel, Italy	161	161	Moretti et al.[25]
Metoclopramide	6	Brazil, Canada, Israel, Italy	175	175	Berkovitch et al.[26]
Methimazole	10	Germany, Israel Italy, France, Netherlands	241	1089	DiGianantonio et al.[27]
Venlafaxine	7	Brazil, Canada, Italy, USA	150	300	Einarson et al.[28]

Source: Medication safety in pregnancy and breastfeeding; Gideon Koren (Ed.), McGraw-Hill 2007

REGULATORY GUIDANCE

ICH M3 (R2) CPMP/ICH/286/95 June 2009

11.4 Pregnant Women
Before the inclusion of pregnant women in clinical trials, all female reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition, safety data from previous human exposure should be evaluated.

Health Canada GUIDANCE DOCUMENT DRAFT - January 9, 2012
"Consideration for Inclusion of Women in Clinical Trials and Analysis of Data by Sex"

2.5 Inclusion of Pregnant and Breastfeeding Women in Clinical Studies/Trials

Post-market Studies:

2.5.1 As is currently the case, it is anticipated that most studies regarding the safety and efficacy of therapeutic products in pregnant or breastfeeding women will be carried out following initial marketing for use in the general population. The use of various methodologies to gather data pertaining to the effects of therapeutic product use in pregnant and breastfeeding women is strongly encouraged. This would include monitoring the outcome of a pregnancy with regard to the health of the women and of the child, in the short and longer term. Such methodologies may include: observational studies, including pregnancy registries and cohort studies; case control studies; case reports; database linkages; and interventional studies such as pharmacokinetic studies and foetal therapy studies.

2.5.2 Post-marketing studies are useful but may not provide all information necessary to inform health care decisions for pregnant and breast feeding women. **Clinical trials are needed to fill the gap, where appropriate**.
There are circumstances in which consideration should be given to including pregnant or breastfeeding women in clinical studies, including clinical trials. In the vast majority of cases, studies will be conducted in pregnant or breastfeeding women already prescribed and taking the medication, hence such studies will not further increase foetal risks.

Considerations for Including Pregnant Women in Clinical Trials

2.5.3 A decision to enrol pregnant women in a specific trial must be individualized and based on a careful risk/benefit assessment taking into consideration: the nature and severity of the disease; the availability and results of previous nonclinical data on pregnant and non-pregnant animals, and results from clinical data; the availability of alternative therapy/therapies and knowledge about their associated risks; the stage of pregnancy in relation to overall development of the foetus, especially regarding foetal brain development; and the potential for harm to the woman, the foetus or child.

2.5.4 **A key consideration in the study of therapeutic products used by pregnant women will be follow-up of the pregnancy, foetus and child. Longer term follow-up of a child is recommended when possible**.

2.5.5 Sponsors may consider including pregnant women in clinical studies, including clinical trials under the following circumstances:

(i) The specific use of the therapeutic product is for pregnant or breastfeeding women (e.g. for obstetrical or pregnancy related problems).

(ii) The studies are of agents which can be expected to address an unmet maternal /foetal risk or disease (e.g. pregnant women with HIV; other life threatening conditions) and where there are no alternatives available on the market.

(iii) **The studies are of agents which can be expected to improve maternal/foetal outcomes as compared to existing therapy**.

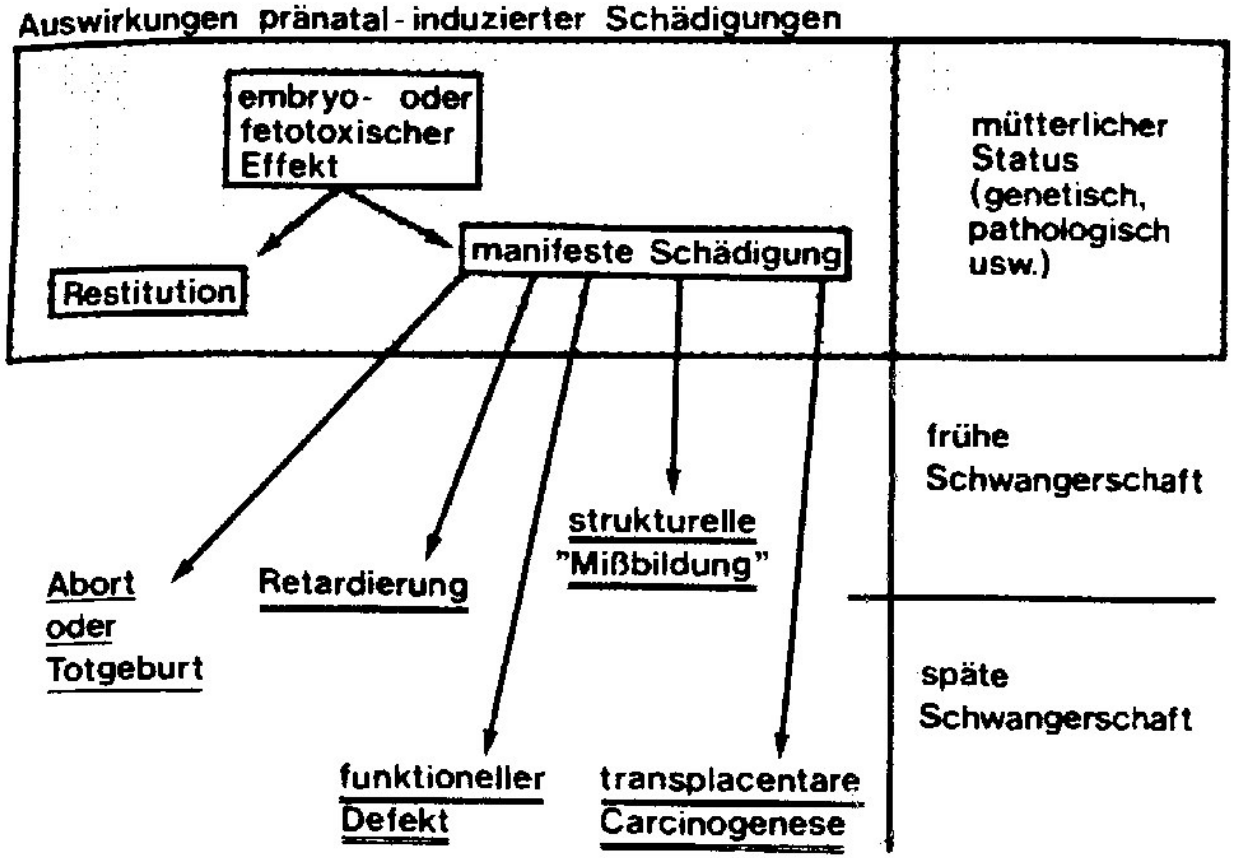
(iv) Animal studies have been conducted, including studies on pregnant animals, and there is data on non pregnant women on which to base an estimate of risk to the woman and/or foetus.

(v) For a new drug or new indication there is anticipated or actual use of the drug in pregnant women and women of childbearing potential.

(vi) The woman and/or foetus will benefit directly from participation and where any potential benefit to the foetus should be weighed against possible risks to the mother.

(vii) The risk to the foetus is not greater than that from established procedures routinely used in an uncomplicated pregnancy, or in a pregnancy with complications comparable to those being studied, and the purpose of the research is the development of biomedical knowledge which cannot be obtained by any other means.

What do we know about potential risks of drugs in pregnancy?



Source: Neubert D; Internist 1978; 19: 304-309

Cave: Retardierung: small for gestational age (SGA)
Cave: Poor neonatal adaptation syndrome (PNAS)

Fetalzeit und spätere Gesundheit

Das Beispiel intrauterine Wachstumsrestriktion

Ernst Beinder

ZUSAMMENFASSUNG

Einleitung: Der Einfluss einer gestörten Fetalzeit auf das Jahrzehnte spätere Auftreten von Erkrankungen wird wissenschaftlich kontrovers diskutiert. Methoden: Literatursuche in Medline mit selektiver Literaturaufarbeitung durch den Autor. Ergebnisse: Die vorhandenen retrospektiven epidemiologischen Untersuchungen haben methodische Mängel, sodass sie einen Kausalzusammenhang zwischen der Fetalzeit und der späteren Gesundheit nicht beweisen können. Sie legen aber in ihrer Gesamtheit eine Verbindung zwischen gestörtem intrauterinen Milieu und Typ-2-Diabetes-mellitus, Herz-Kreislauf-Erkrankungen und weiteren Krankheiten im späteren Leben nahe. Pathophysiologische Studien zeigen, dass sich der Fetus an ein gestörtes intrauterines Milieu mit metabolischen, endokrinen und hämodynamischen Veränderungen adaptiert. Dies geht mit der Umstrukturierung von Arterienwänden, Insulinresistenz und erhöhten Cortisolwerten einher. Diese Faktoren erhöhen bei Persistenz nach der Geburt das Risiko für Herz-Kreislauf-Erkrankungen und Typ-2-Diabetes-mellitus. Diskussion: Falls die Forschung das gestörte intrauterine Milieu als Risikofaktor für Erkrankungen im späteren Leben bestätigt, könnten sich künftig mannigfaltige Ansätze zur primären und früh einsetzenden Prophylaxe dieser Erkrankungen bei entsprechend exponierten Neugeborenen ergeben.

Dtsch Arztebl 2007; 104(10): A 644–50.

Schlüsselwörter: Plazentainsuffizienz, Fetalzeit, Programmierung von Erkrankungen, Hypertonie, kardiovaskuläre Erkrankungen

SUMMARY

INBORN, BUT NOT HEREDITARY: THE IMPORTANCE OF INTRAUTERINE LIFE FOR ADULT DISEASES

Introduction: Epidemiologic studies in a number of different populations have shown an association between low birth weight and the occurrence of hypertension, type 2 diabetes mellitus, arteriosclerosis and mental diseases later in life. It is the aim of this review to present the controversial discussion on this topic. Methods: Medline search and selective literature review. Results: Most of the studies compromise a heterogeneous population of low birthweight infants including preterm and intrauterine growth restricted infants, and healthy, term neonates with low birthweight. Studies suggest that the fetus adapts to an adverse intrauterine environment with metabolic, endocrine and hemodynamic changes which, if they persist into adult life, predispose to hypertension and type 2 diabetes. Discussion: If the effect on adult health of an adverse intrauterine environment is confirmed as an independent effect, the implications for health care systems and on primary prevention of cardio-vascular diseases and type 2 diabetes mellitus in persons born with intrauterine growth restriction is immense.

Dtsch Arztebl 2007; 104(10): A 644-50.

Key-words: placental insufficiency, fetal origin, programming of disease, hypertension, cardiovascular diseases

Examples of pertinent randomised controlled studies in pregnant women

Cochrane Database Syst Rev. 2010 Dec 8;(12):CD000127.

Magnesium sulphate versus diazepam for eclampsia.

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Abstract

BACKGROUND: Eclampsia, the occurrence of a seizure in association with pre-eclampsia, remains a rare but serious complication of pregnancy. A number of different anticonvulsants are used to control eclamptic fits and to prevent further fits.

OBJECTIVES: The objective of this review was to assess the effects of magnesium sulphate compared with diazepam when used for the care of women with eclampsia. Magnesium sulphate is compared with phenytoin and with lytic cocktail in other Cochrane reviews.

SEARCH STRATEGY: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2010) and CENTRAL (2010, Issue 3).

SELECTION CRITERIA: Randomised trials comparing magnesium sulphate (intravenous or intramuscular administration) with diazepam for women with a clinical diagnosis of eclampsia.

DATA COLLECTION AND ANALYSIS: Two authors assessed and extracted data independently.

MAIN RESULTS: We have included seven trials, involving 1396 women. Three trials (1030 women) were good quality. Magnesium sulphate was associated with a reduction in maternal death (seven trials;1396 women; risk ratio (RR) 0.59, 95% confidence interval (CI) 0.38 to 0.92) and recurrence of seizures (seven trials;1390 women; RR 0.43, 95% CI 0.33 to 0.55) compared to diazepam. There were no clear differences in other measures of maternal morbidity.There was no clear difference in perinatal mortality (four trials; 788 infants; RR 1.04, 95% CI 0.81 to 1.34) or neonatal mortality (four trials; 759 infants; RR 1.18, 95% CI 0.75 to 1.84). In the magnesium sulphate group, fewer liveborn babies had an Apgar score less than seven at one minute (two trials; 597 babies; RR 0.75, 95% CI 0.65 to 0.87) or at five minutes (RR 0.70, 95% CI 0.54 to 0.90), and fewer appeared to need intubation at the place of birth (two trials; 591 infants; RR 0.67, 95% CI 0.45 to 1.00). There was no difference in admission to a special care nursery (four trials; 834 infants; RR 0.91, 95% CI 0.79 to 1.05), but fewer babies in the magnesium sulphate group had a length of stay more than seven days (three trials 631 babies; RR 0.66, 95% CI 0.46 to 0.96).

AUTHORS' CONCLUSIONS: Magnesium sulphate for women with eclampsia reduces the risk ratio of maternal death and of recurrence of seizures, compared with diazepam.

Cochrane Database Syst Rev. 2010 Oct 6;(10):CD000128.

Magnesium sulphate versus phenytoin for eclampsia.

Duley L, Henderson-Smart DJ, Chou D.

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SELECTION CRITERIA: Randomised trials comparing magnesium sulphate (intravenous or intramuscular administration) with phenytoin for women with a clinical diagnosis of eclampsia.

DATA COLLECTION AND ANALYSIS: Two review authors assessed trial quality and extracted data.

MAIN RESULTS: We have included data from seven trials, involving 972 women. One large trial (775 women) was of good quality. Magnesium sulphate was associated with a substantial reduction in the recurrence of seizures, when compared to phenytoin (six trials, 972 women; risk ratio (RR) 0.34, 95% confidence interval (CI) 0.24 to 0.49). The trend in maternal mortality favours magnesium sulphate, but the difference does not reach statistical significance (three trials, 847 women; RR 0.50, 95% CI 0.24 to 1.05). There were reductions in the risk of pneumonia (one trial, RR 0.44, 95% CI 0.24 to 0.79), ventilation (one trial, RR 0.68, 95% CI 0.50 to 0.91) and admission to an intensive care unit (one trial, RR 0.67, 95% CI 0.50 to 0.89) associated with the use of magnesium sulphate rather than phenytoin.For the baby, magnesium sulphate was associated with fewer admissions to a special care baby unit (SCBU) (one trial, 518 babies; RR 0.73, 95% CI 0.58 to 0.91) and fewer babies who died or were in SCBU for more than seven days (one trial, 643 babies; RR 0.77, 95% CI 0.63 to 0.95) than phenytoin. There was no clear difference in perinatal deaths (two trials, 665 babies; (RR 0.85, 95% CI 0.67 to 1.09).

AUTHORS' CONCLUSIONS: Magnesium sulphate, rather than phenytoin, for women with eclampsia reduces the risk ratio of recurrence of seizures, probably reduces the risk of maternal death, and improves outcome for the baby. Magnesium sulphate is the drug of choice for women with eclampsia. The use of phenytoin should be abandoned.

Update of

Cochrane Database Syst Rev. 2003;(4):CD000128.

Control of mild to moderate hypertension in pregnancy:
Meta-analysis of 45 randomised controlled trials (n=3773 women)
including seven trials using a placebo control/no treatment

Lancet. 2000 Jan 8;355(9198):87-92.

Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis.

von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA.

Department of Obstetrics and Gynaecology, University of Toronto, Canada.

Abstract

BACKGROUND: We investigated the relation between fetoplacental growth and the use of oral antihypertensive medication to treat mild-to-moderate pregnancy hypertension.

METHODS: The study design was a metaregression analysis of published data from randomised controlled trials. Data from a paper that was regarded as an extreme statistical outliner were excluded from primary analyses. The change in (group) mean arterial pressure (MAP) from enrolment to delivery was compared with indicators of fetoplacental growth.

FINDINGS: Greater mean difference in MAP with antihypertensive therapy was associated with the birth of a higher proportion of small-for-gestational-age (SGA) infants (slope: 0.09 [SD 0.03], r2=0.48, p=0.006, 14 trials) and lower mean birthweight significant after exclusion of data from another paper regarded as an extreme statistical outliner (slope: -14.49 [6.98] r=0.16, p=0.049, 27). No relation with mean placental weight was seen (slope -2.01 [1.62], r2=0.15, p=0.25, 11 trials).

INTERPRETATION: Treatment-induced falls in maternal blood pressure may adversely affect fetal growth. Given the small maternal benefits that are likely to be derived from therapy, new data are urgently needed to elucidate the relative maternal and fetal benefits and risks of oral antihypertensive drug treatment of mild-to-moderate pregnancy hypertension.

Conclusions:

- Pregnant women have been amply enrolled in post-marketing studies; see TIS activities.
- Regulatory guidance supports the inclusion of pregnant women in clinical trials; this includes randomised controlled trials; criteria for the selection of drugs have been set up; the nonclinical and clinical amount of data required have been defined. Drugs not to be used in pregnant women or with a known or highly suspect foetal risk should not be investigated.
- There are numerous, pertinent examples of randomised controlled trials in pregnancy.
- These trials specified improved treatment regimens with better outcomes for mother and child.
- More studies are required with respect to risk assessment /risk-benefit assessment of drugs in pregnancy