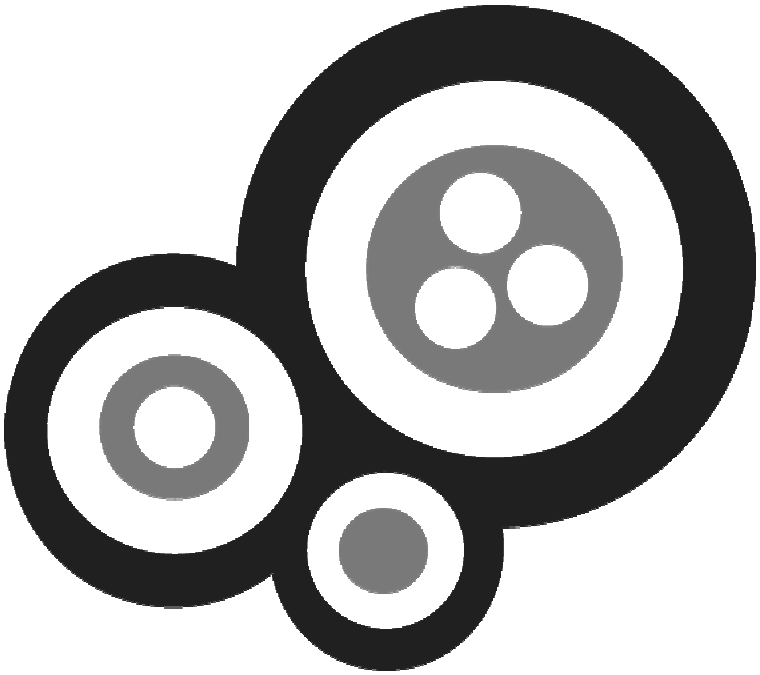

BREAKOUT 3

EXPOSURES AND PREGNANCY OUTCOMES

Moderators:
Christina Chambers – USA
Eduardo Castilla – Brazil

POSTMARKETING DRUG TERATOLOGY SURVEILLANCE IN HUNGARY: A SUCCESSFUL MODEL

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Clinical trials conducted before approval and marketing of a drug generally cannot include pregnant women. It is necessary therefore to base the potential for human risk mainly on the results of experimental animal investigations; however, species and other differences preclude the direct extrapolation of these results to humans. Thus, the harsh reality is that humans are the ultimate test model fro the detection of drugs and doses of drugs that are human teratogens. Two types of postmarketing data are used to estimate the human teratogenic potential of drugs. The first type includes case reports, clinical case series and randomized controlled trials. However, case reports have serious selection bias, clinical case series usually do not have appropriate controls and there are ethical barriers to perform randomized controlled trials in pregnant women. The second type of data sets is analytical epidemiological studies and/or registry/surveillance/monitoring systems.

The Hungarian Congenital Abnormality Registry was established in 1962 and later detected some time/spatial clusters of cases with different structural birth defects, i.e. congenital abnormalities (CAs). The data of registries are not able to detect the causes of CA clusters, and after it, to prevent this excess of cases; therefore we had to organize time and money consuming *ad hoc* case-control epidemiological studies to detect the causes of these CA clusters. This fact stimulated us to establish the Hungarian Case-Controls Surveillance of Congenital Abnormalities in 1980 based on the comparison of cases with CA selected from our registry and controls without any defects selected from the National Birth Registry. Two or three controls were matched to each case according to sex, birth week and district of parents' residence. Exposure and confounder data were obtained from three sources: (i) Prenatal logbooks and other medical documents containing prospective and medically recorded exposures (e.g. drug uses). (ii) A structured questionnaire including retrospective maternal information. (iii) All non-respondent mothers of cases and 200 mothers of controls were visited at home by regional nurses to obtain the necessary data. At the evaluation of our population-based data (1) we neglect the unscientific first trimester concept, the exposures are evaluated on the specific critical period of each CA; (2) we differentiate 25 CA groups and if we can find some association with a suspected teratogenic or fetotoxic exposure, we do our best to use CA entities as homogeneous as possible from etiological aspect; (3) exposures are also splitted as much as possible, thus we do not combine antibiotics, sulfonamides, etc but we evaluate specific drugs separately; (4) we evaluate the fetotoxic effect (e.g. intrauterine fetal growth retardation) of drugs as well beyond their teratogenic effect; and finally (5) we consider all possible confounders in the conditional logistic regression model.

TELEPHONE-BASED EXPOSURE RISK ASSESSMENT AND COUNSELING TO IMPROVE PREGNANCY OUTCOMES– THE TERATOGEN INFORMATION SERVICE MODEL IN THE U.S. AND CANADA

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Teratology Information Services (TIS) provide women and their caregivers with information on prenatal and lactation exposures to a variety of agents. Depending on TIS scope and structure, they may provide advice on topics including medication use, environmental exposures, genetics, disease and addiction in pregnancy, and nutritional supplementation. This information is primarily provided through telephone call centers located in hospitals or university-based settings. The most commonly recognized result of information received from TIS is reduction in maternal anxiety. This may lead to continuation or compliance with needed therapy and therefore benefit pregnancy outcome. TIS can help to prevent congenital malformations, and can prevent unnecessary pregnancy terminations and occupational risks by providing information that changes behavior. TIS improve risk perception and facilitate knowledge transfer and translation to health care providers. TIS in the U.S. and Canada also contribute to the body of research on exposures risks in pregnancy through collaborative and individually sponsored prospective studies. Although U.S. and Canadian TIS provide risk assessment and counseling to over 70,000 callers per year, less than 10% of caller contacts are from women who are planning a pregnancy. Thus, preconception counseling is an opportunity area for TIS.

PRECONCEPTIONAL CARE: FIVE YEARS EXPERIENCE OF A TERATOLOGY INFORMATION SERVICE

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Objective: To evaluate the main preconceptional risk factors, prevalence of chronic maternal diseases and the attitude to acid folic supplementation in a selected population calling to an Italian Teratology Information Service.

Method: A descriptive study on 2405 callers asking for preconceptional care to an Italian Teratology Information Service, was performed between 2002 and 2006.

Result: Preconceptional drug exposure is the main reason for calling and teratogen drugs accounted for 24% of total drugs.

There was an high prevalence of chronic pathologies (54%), which was mainly neurologic disease (70%).

Folic acid was assumed only in 54% of the women at the moment of the call.

In the subpopulation of the epileptic women only 12% were taken folic acid.

Conclusion: Drug exposure is responsible of the high population's awareness as risk factor for pregnancy. Teratogen drugs exposure and chronic diseases prevalence are significantly represented among calling population and could enhance the risk of poor pregnancy outcome. Prevalence of preconceptional folic acid supplementation is still low and could be improved, especially in high risk population, such as epileptic women.

Teratology Information Service supports general health population throughout preconceptional care and could improve pregnancy outcome, mainly in high risk population affected by chronic diseases and often treated with teratogenic drugs, reducing birth defects risks.

WORKING CONDITIONS AND PRECONCEPTION CARE

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A lot of factors can influence the outcome of pregnancy and result in pregnancy complications like spontaneous abortion, preterm birth, low birth weight or congenital malformations. Working conditions are among environmental risk factors that can have a negative impact on pregnancy outcomes, but to date relatively little attention has been paid on working conditions of women during their (early) pregnancy or before conception.

During recent years, increasing attention has been paid on preconception care as a means of promoting the health of parents to be and their future children. It was this trend together with a relatively high perinatal mortality in the Netherlands, that prompted the Minister of Health, Welfare and Sport to ask for an advisory report on preconception care by the Dutch Health Council. For this report also a literature study was carried out on working conditions. The results of this study are published as a chapter in the report, and will be presented at this congress.

Exposure to high concentrations of chemical agents is detrimental to the health of all people. This is particular relevant to people who are trying to conceive and women who are pregnant, because of the possible adverse effects on fetal growth and development. There are indications that exposure to high concentrations of such compounds as pesticides, solvents, cytostatics and probably also some anesthetics is associated with an increased risk of miscarriage and congenital malformations. Emotional and physical stress around conception can also be harmful and can lead to an increased risk of spontaneous abortion.

On the basis of this literature study it is advised that pregnant women but also couples trying to conceive should not be exposed to genotoxic substances, like mutagenic and most of the carcinogenic substances. These kind of working conditions related risks should be implemented in programs of preconception care, next to counseling concerning medical- and life-style risks like smoking and malnutrition.

Reference: *Health Council of the Netherlands. Preconception care: a good beginning. The Hague: Health Council of the Netherlands, 2007; publication no.2007/19*

CHRONIC EXPOSURE TO RADIONUCLIDES IN ANIMALS LIVING IN THE SHADOW OF CHERNOBYL: LESSONS FOR HUMAN POPULATIONS?

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Background: There is considerable controversy concerning the health consequences of chronic exposure to low dose ionizing radiation. Many prominent reports (e.g. the Chernobyl Forum 2006) have suggested that there is no evidence for significant health effects. Studies of natural populations of plants and animals living in the shadow of the Chernobyl contamination plume provide a unique opportunity to investigate the genetic and fitness consequences of low-dose contaminants. Such studies should have relevance for human populations living in the contaminated regions of Ukraine, Belarus and Russia, and may be useful for hazard assessment related to industrial, military or terrorist nuclear incidents in the future.

Methods and Results: We have studied the birds of Chernobyl since 2000 and insect populations since 2005. Studies of barn swallows (*Hiundo rustica*) have revealed that Chernobyl populations display significantly increased mutation rates that are expressed as increased rates of morphological deformitaties, sperm deformities and decreased sperm performance, reduced reproductive success, and significantly lower annual survival rates (< 20% in Chernobyl vs. > 40% in control populations). Additional studies of other bird species, and other animals suggest that many organisms are negatively impacted by radioactive contaminants.

Conclusions: These studies suggest that many species show affects of contaminants on performance, even in populations with low contamination levels where conventional wisdom might suggest that there should be minimal or no effects. These results should be considered when addressing policy related to hazard assessment stemming from nuclear incidents and they point to the need for further research on the health consequences of low dose radiation.

PREGNANCY OUTCOME AFTER PRECONCEPTIONAL VAGINAL MICRONIZED PROGESTERONE IN RECURRENT PREGNANCY LOSS

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Objectives: Pregnancy outcome after preconceptional to 36 weeks gestation of folic acid (FA) and vaginal micronized progesterone (VMP) in recurrent pregnancy loss

Methods: Two patients groups enrolled if accomplished inclusion/exclusion criteria (different by moment of 2 previous pregnancy loss: first trimester – group A, third trimester – group B), 6 months preconceptional treated with folic acid 1 mg/day, 200 mg vaginal micronized progesterone (14 days/month, luteal phase), continued after positive pregnancy test to 36th weeks, and a control group (C) on *placebo*. Ultrasonographic examination between 12-20 weeks 6 days to confirm gestational age (GA), and malformations screening, repeated at 32 to 34 weeks. Outcome measures: *primary*: birthweight, Apgar scores, congenital malformations, GA of preterm birth, composite neonatal morbidity, oxygen supplementation, mechanic ventilation, sepsis, death before discharge; *secondary*: moment of miscarriage, maternal weight gain, and morbidity; hospitalizations for threaten of miscarriage/preterm birth.

Statistics analysis: Student test for comparison of treated to controls, ANOVA method.

Results: During 12 months/2007 were prospectively registered 38 cases (32 – group A, 6 – group B), 58 controls. Patients' characteristics: Age: controls: 26.9±4.77, group A: 31.33±4.54 (P=.038), group B: 31.33±4.54 (P=.038); Gestation: controls: 4.76±3.42; group A: 3.82±2.53 (P=.26), group B: 3.83±2.31 (P=.52); Parity: controls: 2.17±1.22, group A: 1.5±0.59 (P=.005), group B: 1.67±0.81 (P=.33); Preconception Weight: controls: 55.32±7.39, group A: 58.59±9.27 (P=.13), group B: 61.33±12 (P=.09); Weight Gain: controls: 11.95±4.75, group A: 16.77±5.71 (P=.001), group B: 14.33±3.32 (P=.24)

Primary outcomes: Delivery Fetal Weight: controls: 2506.1±699.21 g, group A: 3100±489.41 g (P=.001); group B: 3216± 537.27 g (P=.022), with 4 cases <1500 g in controls, 0 treated, and <2500 g: 16 controls, 1 group A (P=.0001); Apgar Scores: 1/5 minutes: controls: 8.05±1.98/8.2±1.99, group A: 8.45±1.53 (P=.40)/8.77±1.11 (P=.21), group B: 4.83±4.57 (P=.14)/4.83±4.62 (P=.13); pH Blood Cord when Apgar <7/1 minute: controls: 7.20±0.19, group A: 7.14±0.34 (P=.81), group B: 6.55±0 (P=.0001). GA at delivery: 24-28 weeks (0/0/2 in group A/B/C); 29-34 weeks (1/1/16 in group A/B/C); ≥ 35weeks (21/5/23 in groups A/B/C).

Malformations: 2 hypospadias (group A, control), criptorhydria (1 control), hydrocele: (1 control), umbilical hernia (1 control), neonatal morbidity: Respiratory Distress Syndrome: 2/1/5 (group A/B/C), no: Bronchopulmonary Dysplasia, Intraventricular Haemorrhage, Necrositing Enterocolitis.

Secondary outcomes: 25 miscarriges (first trimester: 9/0/13 in group A/B/C; second trimester: 3/0/3 in group A/B/C); 4 stillbirth (0/2/2 in group A/B/C); 4 fetal deaths before discharge (0/2/2 in group A/B/C); gestational hypertension [group B: 2(7.1%), controls: 3(19%)], no gestational diabetes; hospitalization for threaten abortion (8 among those who delivered, vs 20 controls) / preterm birth (10 treated vs 18 controls)

Conclusion: FA&VMP preconceptional, in early and late pregnancy in recurrent pregnancy loss are followed by a significant reduction of preterm birth before 34 weeks (13.6% treated vs 36.6% controls), a reduction of miscarriges (23.7% treated vs 27,7% controls), an increase of birthweight (P=.001, group A; P=.022 group B), less cases with reduced blood cord pH (P=.0001 - group B) when Apgar score <7/1minute, less neonatal morbidity (only RDS: 10.3% treated vs 12.2% controls), a nonsignificant difference in perinatal mortality; 2 cases with hypospadias (groupA, controls), more other abnormalities in controls. Gestational hypertension was significantly lower in treated (7.1%) vs controls (19%), no gestational diabetes, less hospitalization for abortion threaten (28.6% treated vs 48.8 controls)/preterm birth (35.1% studied vs 43.8% controls).