Maternal - Infant Biomonitoring: The Epidemiological Challenges

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Why Biomonitoring of Pregnant Women and/or Infants?

- Most susceptible sub-population to effects of environmental contaminants
- Different exposure patterns (sources, levels)
- Under-represented (not included) in general population surveys

Unique Challenges

- Recognize that there are critical time periods of exposure or susceptibility
  - Embryo/fetal/infant development
  - Impact of pregnancy and stage of pregnancy on ADME of chemicals
- Difficult to obtain representative sample
  - Pregnancies
    - Would take considerable effort to identify sample at same stage of pregnancy (e.g., random digit dialling)
  - Births
    - Proportion of births outside hospital may vary by region, SES, culture

Options for Identifying Survey Population of Pregnant Women

- Extensive screening of large random sample of population
  - What percentage of general population would be X weeks pregnant?
  - Recognize that during time lag between identification, recruitment and sampling, pregnancy is advancing (or lost)
    - May not be able to collect an early pregnancy sample
    - Awareness of pregnancy varies by individual
    - Is the survey sample truly representative?

Options for Identifying Survey Population of Pregnant Women

- Self identification through advertisements
  - May be selection biases if women of certain education, culture or economic status are more likely to see ads and volunteer
- Access women through health care providers
  - Select through some kind of sampling process
  - If poor participation/cooperation by health care providers, will sample be representative?
- Use established national clinical research networks
  - Experienced in recruitment, data/specimen collection

Options for Identifying Population of Newborns

- Sampling of hospitals
  - Non-hospital births not represented
    - Might be able to work with groups of midwives
  - Likely to miss short hospital stays (healthy mothers/babies)
  - Must establish relationships with hospital and labor/delivery room staff
  - Survey staff on call 24/7
- Other options???

Unique Challenges

- Biospecimen collection
  - Not general healthy population but pregnant women and/or newborns
    - May have health problems during pregnancy
    - Pregnancy may be terminated or lost
    - Biospecimen collection may cause anxiety
    - May have to deal with health care providers and hospitals
  - When should sample be collected?
    - Stage of pregnancy and/or at birth

Unique Challenges of Biospecimen Collection

- Where should sample be collected?
  - Where woman receives care or at survey site?
- Maternal Blood and Urine
  - Women are routinely asked to provide these samples as part of care
  - How does pregnancy affect concentration of biomarker?
    - Plasma volume expansion – can vary from minimal to 2-fold increase; but difficult to measure in population studies
    - Urinary creatinine

Unique Challenges of Biospecimen Collection

- Cord Blood can be difficult to collect
  - Can not schedule delivery (unless scheduled c-section)
  - Can be a hectic or crisis situation with high likelihood that cord blood collection will be forgotten
  - Contamination by collection materials may be a problem for certain chemicals
  - Competition for sample with other research or stem cell bank
- Maternal Hair

Unique Challenges of Biospecimen Collection

- Meconium
  - the first several stools passed by a newborn after birth
  - begins to form *in utero* around the 13th week of gestation and accumulates thereafter
  - may provide a longer and cumulative record of exposure to various environmental chemicals than urine or cord blood
  - composed of amniotic fluid, mucous, lanugo (the fine hair that covers the baby's body), bile, and cells that have been shed from the skin and the intestinal tract
  - thick, tar-like, greenish black, and sticky
  - noninvasive
  - considered by some an ideal matrix for measuring *in utero* body burdens of contaminants (heavy metals, cotinine, POPs, OP pesticides, pyrethroids)

Unique Challenges of Biospecimen Collection

- Meconium collection
  - Recent pilot study showed evidence that concentration of biomarker may change with serial samples
  - Options
    - Collect serial samples and analyze separately
      - Expensive, but may provide exposure relevant to critical periods of gestation
    - Pool all meconium from newborn
  - Concern about contamination of sample by diapers, urine

Unique Challenges of Biospecimen Collection

- Neonatal hair
  - May not be any/enough
- Urine
  - Requires special diapers
- Vernix
  - Waxy material protecting skin of newborns
  - ?
- Nail clippings

Unique Challenges of Biospecimen Collection

- Breast milk
  - Not all women breastfeed
  - Women may have difficulty providing extra milk for sampling
  - Potential contamination by collection materials if breast pump used (can be difficult to hand express)
  - Standardizing collection
    - Time of day, all from one breast or serial collection from both breasts, mixture of hind and fore milk

MIREC

Maternal-Infant Research on Environmental Chemicals:

A National Profile of *In Utero* and Lactational Exposure to Environmental Contaminants

MIREC

Maternal-Infant Research on Environmental Chemicals

Étude mère-enfant sur les composés chimiques de l'environnement

Funding agencies
Health Canada
Ontario Ministry of the Environment
Canadian Institutes of Health Research

Project initiated by Health Canada,
in collaboration with CHU Ste-Justine

Organismes subventionnaires
Santé Canada
Ministère de l'Environnement de l'Ontario
Instituts de recherche en santé du Canada

Une initiative de Santé Canada,
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Health Canada | Santé Canada

Ontario

IRSC CIHR

CHU Sainte-Justine

Mother and Child University Hospital Center | *Le centre hospitalier universitaire mère-enfants*

For the love of children | *Pour l'amour des enfants*

Université de Montréal

Background on Design

- Unique combination of surveillance and research
- Looked for ongoing national-level pregnancy studies to which we could add environmental biomonitoring
- Found large clinical trial of anti-oxidant vitamin supplementation and risk of preeclampsia
- Literature search of environmental chemicals potentially associated with gestational hypertension or preeclampsia
- Wrote grant application for ancillary study focussing on heavy metal exposure

Background on Design

- Clinical trial stopped during grant review period
- Grant was funded but now no cohort
- Search for funding within Health Canada
- Food Directorate planning national breast milk survey
- Tobacco Control Programme needs data on smoking and treatment programmes during pregnancy
- Federal Government announces Chemical Management Plan with funds for biomonitoring
- Canadian Health Measures Survey (ages 6 plus)
- Creation of new national-level pregnancy cohort to obtain data on prenatal and lactational exposure to priority environmental chemicals

MIREC Objectives

- To determine if heavy metal exposure is related to elevated maternal blood pressure, hypertension, altered sex ratio and fetal growth retardation
- To obtain national-level data on maternal and neonatal exposure to priority environmental contaminants
- To obtain Canadian data on smoking behaviour and exposure to tobacco smoke (active and passive) in pregnancy

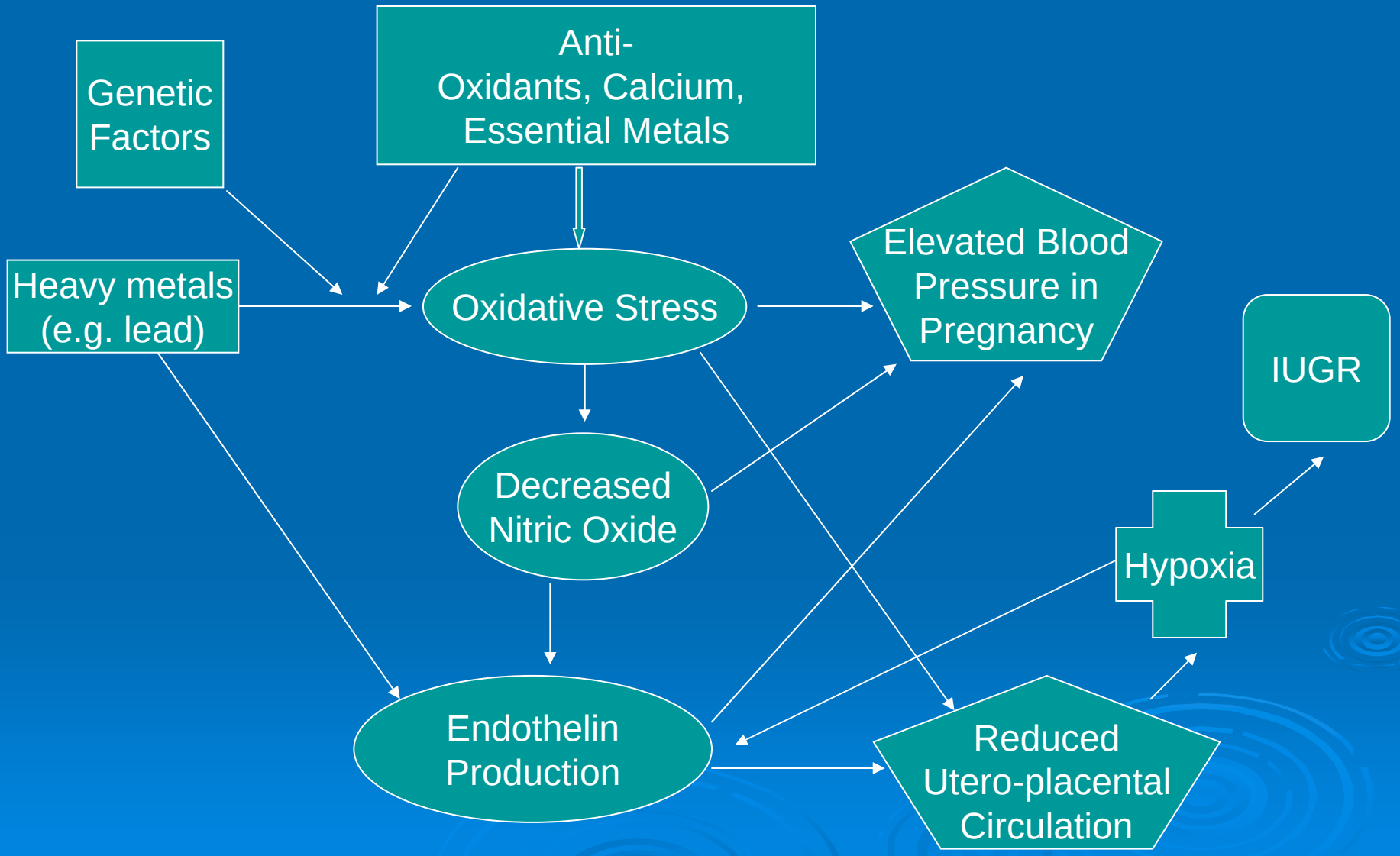
Objectives

- To obtain contemporary levels of priority environmental chemicals, selected nutrients and relevant immunoprotective endpoints in mature human milk
- To allow for time-trend analyses for those analytes which were included in previous human milk surveys
- To obtain contemporary levels of maternal hair-mercury

Secondary (Exploratory) Objectives

- To measure the distribution of pre- and post-natal body burdens of heavy metals in a population of Canadian women over the course of pregnancy, examine the correlation between maternal and fetal body burdens, and identify factors that affect the concentration of heavy metals in newborn infants (as measured by cord blood and meconium analyses)
- To investigate possible avenues for secondary prevention against metal-induced toxicity (e.g., antioxidant vitamins, calcium, selenium)
- To explore candidate genetic polymorphisms that may explain differences in susceptibility to metals toxicity
- To elucidate the oxidative stress pathways by analysing specific metabolic biomarkers and examining their association with heavy metal concentrations in maternal blood as well as associations with vasoregulatory components such as the plasma endothelins and free nitrite levels

Figure 1: Proposed Model of Role of Heavy Metals, Nutrition and Oxidative Stress in Pregnancy Outcomes



Secondary (Exploratory) Objectives

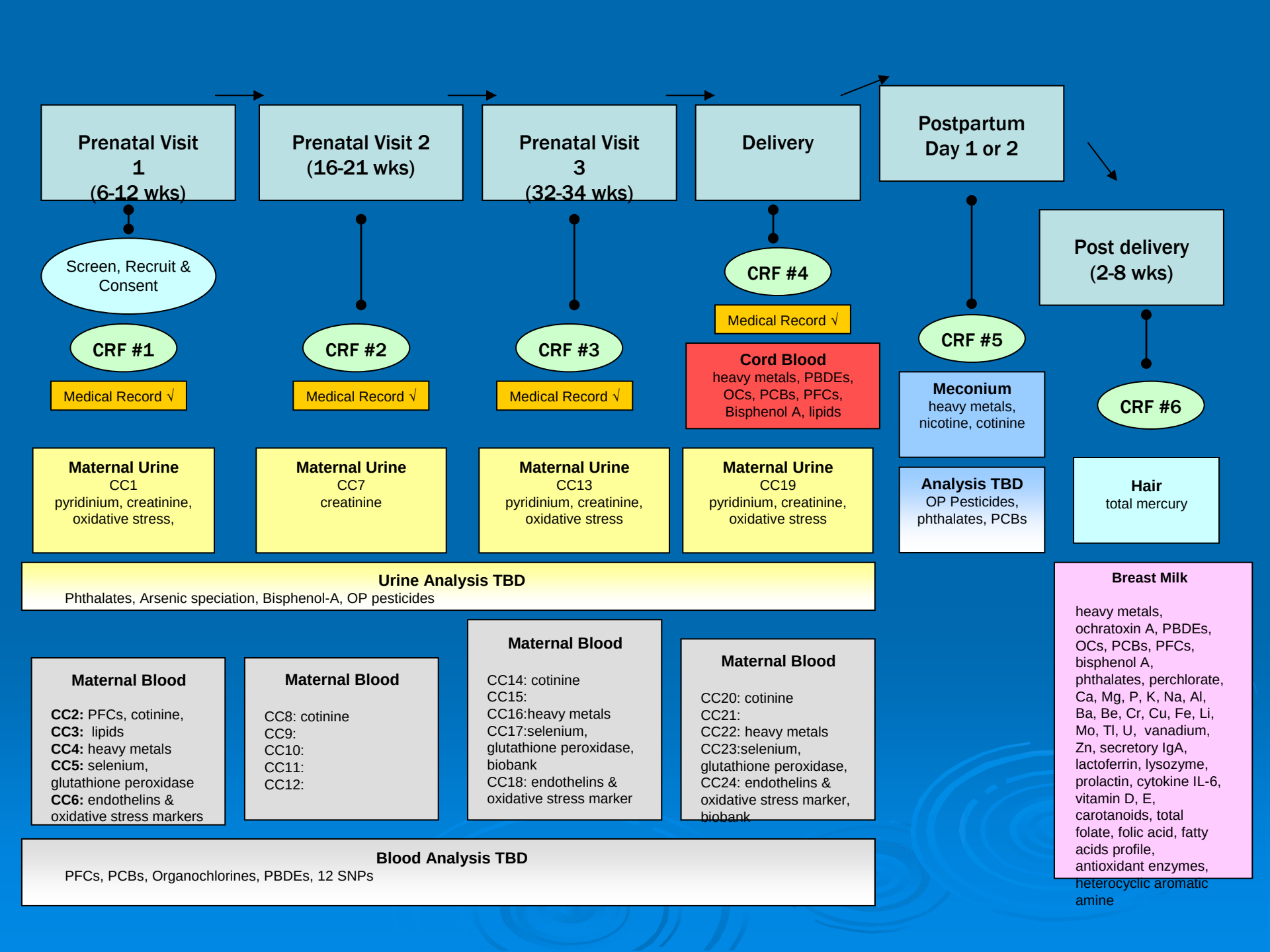
- To identify potential sources of exposure, as well as predictors of exposure to environmental chemicals
- To identify environmental and maternal dietary and lifestyle factors which correlate with levels of nutrients, environmental chemicals and immunoprotective constituents in human milk
- To examine the correlations between environmental chemicals and nutrients in human milk
- To examine the correlations between environmental chemicals and immunoprotective constituents in human milk
- To undertake a comprehensive risk:benefits analysis for human milk

Study Design

- A new national-level pregnancy cohort
- Approximately 2,000 pregnant women
- Recruited during 1st trimester
- Clinical sites across Canada (Vancouver, Calgary, Winnipeg, Sudbury, Ottawa, Kingston, Hamilton, Toronto, Montreal, Halifax)
- Each site led by clinical research (obstetrician)

Selection of Chemicals for Biomonitoring

- Sub-set of chemicals from Canadian Health Measures Survey
- Potential for reproductive toxicity and/or endocrine modulation
- Feasibility
- Heavy metals, plasticizers, BFRs, OP pesticides, PFCs, cotinine


Prenatal Visit 1 (6-12 wks)
Prenatal Visit 2 (16-21 wks)
Prenatal Visit 3 (32-34 wks)
Delivery
Postpartum Day 1 or 2
Post delivery (2-8 wks)
Screen, Recruit & Consent
CRF #1
CRF #2
CRF #3
CRF #4
CRF #5
CRF #6
Medical Record √
Medical Record √
Medical Record √
Medical Record √
Cord Blood
heavy metals, PBDEs, OCs, PCBs, PFCs, Bisphenol A, lipids
Meconium
heavy metals, nicotine, cotinine
Analysis TBD
OP Pesticides, phthalates, PCBs
Hair
total mercury
Maternal Urine
CC1
pyridinium, creatinine, oxidative stress,
Maternal Urine
CC7
creatinine
Maternal Urine
CC13
pyridinium, creatinine, oxidative stress
Maternal Urine
CC19
pyridinium, creatinine, oxidative stress
Urine Analysis TBD
Phthalates, Arsenic speciation, Bisphenol-A, OP pesticides
Maternal Blood
CC2: PFCs, cotinine,
CC3: lipids
CC4: heavy metals
CC5: selenium, glutathione peroxidase
CC6: endothelins & oxidative stress markers
Maternal Blood
CC8: cotinine
CC9:
CC10:
CC11:
CC12:
Maternal Blood
CC14: cotinine
CC15:
CC16:heavy metals
CC17:selenium, glutathione peroxidase, biobank
CC18: endothelins & oxidative stress marker
Maternal Blood
CC20: cotinine
CC21:
CC22: heavy metals
CC23:selenium, glutathione peroxidase,
CC24: endothelins & oxidative stress marker, biobank
Blood Analysis TBD
PFCs, PCBs, Organochlorines, PBDEs, 12 SNPs
Breast Milk
heavy metals, ochratoxin A, PBDEs, OCs, PCBs, PFCs, bisphenol A, phthalates, perchlorate, Ca, Mg, P, K, Na, Al, Ba, Be, Cr, Cu, Fe, Li, Mo, Tl, U, vanadium, Zn, secretory IgA, lactoferrin, lysozyme, prolactin, cytokine IL-6, vitamin D, E, carotanoids, total folate, folic acid, fatty acids profile, antioxidant enzymes, heterocyclic aromatic amine

How Biomonitoring Data will be Used

- To quantify exposure for estimation of risks
- To provide national level-surveillance data on vulnerable population
  - Complements general population survey
  - Baseline data; identification of sub-populations at increased risk
- Time-trend analysis of breast milk contaminants
- Some source attribution based on questionnaire data
- Analysis of serial measures of heavy metals during pregnancy

Challenges

- Multiple ethics committees !!!!!
  - Consent forms
- Site agreements
- Academic – government partnership
- Privacy laws
- Logistics of
  - Multiple sites/hospitals
  - Multiple labs for analyses (same lab for chemicals)
  - Biobanking
    - Governance policy, space, freezers, cryovials

Challenges

- Reporting of individual results
  - Heavy metal results provided to woman and her physician (if she so requests)
  - Other chemical results optional
  - 2-page information sheet
- Results Report Advisory Committee
  - Risk assessors, communication specialists
  - Develop 2-page information sheet on each chemical or chemical group (e.g. BFRs)
  - Sources of exposure, levels reported in other surveys, potential toxicity, etc.
  - Goal: education NOT assessment of individual risks

Challenges

- Everything takes much longer than expected
- Budget estimates significantly under-estimated
- But hopefully, will have a unique, rich resource to test and generate many hypotheses on role of environmental chemicals in children's health