The Mount Sinai Center for Children’s Health and the Environment  
New York City Department of Health and Mental Hygiene  
Lead Poisoning Prevention Program  

Project to Investigate Lead Poisoning in Pregnant Women  

Work Plan for Systematic Review of the Literature

The review of the literature began with the charge questions which are;

1. Which pregnant women need to be tested for lead poisoning?
   a. What subgroups of pregnant and lactating women are at greatest risk of lead poisoning?
   b. What, if any, questions should be asked by medical providers of all pregnant women to determine whether they are high risk and need testing?
   c. How can LPPP best reach out to medical providers to promote systematic risk assessment and testing of pregnant women at high risk of lead poisoning.

2. What information should medical providers be giving all pregnant women about lead poisoning prevention and, specifically, women at high risk of lead poisoning?

3. What does the current evidence demonstrate regarding the health effects of various degrees of overexposure to lead in pregnant or lactating women and in neonates?
   a. What is the clinical impact on pregnancy outcomes of elevated lead levels?
      i. Stillbirths
      ii. Preterm delivery and gestational age
      iii. Spontaneous abortion
      iv. Birth weight
   b. What is the relationship between blood lead levels and Pregnancy induced hypertension?
   c. What is the clinical impact on neurodevelopment and behavior of prenatal lead exposure?
   d. What is the clinical impact of prenatal lead exposure on head circumference?
   e. What are the blood lead levels at which adverse clinical outcomes are seen?

4. At what blood lead level should minimal intervention such as education or follow-up testing be provided?
   a. By medical providers?
   b. By LPPP?

5. What are the appropriate intervention activities at different blood lead levels (e.g., 10-19 mcg/dL, ≥20 mcg/dL) for health care providers treating lead poisoned women during and after pregnancy?
   a. What educational messages should be provided to lead poisoned pregnant and lactating women?
b. What is the role of medical providers in coordinating environmental risk assessment and intervention with the LPPP?
c. What nutritional counseling should be provided to lead poisoned pregnant and lactating women. Specifically, what are the benefits of calcium and iron supplementation?
d. What should the frequency of re-testing be for pregnant and lactating women and for the neonate?
e. When should chelation be provided for pregnant and lactating women and for the neonate?
f. What postpartum hospital discharge plans should be recommended?

6. What are the appropriate LPPP intervention activities for pregnant women at various blood lead levels (e.g., 10-19 mcg/dL, ≥20 mcg/dL), including environmental assessment of home and risk reduction for pregnant women and other family members?
   a. What type of environmental risk assessment of paint and non-paint lead hazards (e.g., pica, pottery, food sources, traditional remedies, cosmetics, etc) is appropriate at different blood lead levels?
   b. What interventions should be recommended to eliminate or reduce sources of lead? When should lead-based paint hazard reduction be recommended? How should cultural practices among cultural and immigrant groups (e.g., pica, use of pottery, consumption of foods or consumption of supplements) be addressed in a culturally sensitive way?
   c. What counseling should the LPPP be providing to lead poisoned pregnant and lactating women?
   d. How should the LPPP coordinate with medical providers who are serving lead poisoned pregnant and lactating women?

7. What are the barriers that prevent health care providers from systematically assessing risk, testing, providing case management and coordinating care for pregnant and lactating women and newborns?

8. What are the cultural, ethnic and linguistic issues that LPPP staff and health care providers need to be aware of in order to reach and intervene with lead-poisoned pregnant women in NYC?
   a. What are the unique cultural characteristics that place these sub-populations at increased risk of lead exposure?

The charge questions, taken as a whole were then analyzed and broken down into explicit clinical questions. These are:

1. What is the clinical impact on pregnancy outcomes of elevated lead levels?
2. What is the clinical impact of prenatal lead exposure on head circumference?
3. What is the relationship between blood lead levels and PIH?
4. What is the clinical impact on neurodevelopment and behavior of prenatal lead exposure?
5. When is the most appropriate time to measure blood lead levels in pregnant women and neonates?
6. How effective are screening questionnaires for detecting pregnant women with elevated lead levels?
7. What is the predicted prevalence of elevated lead levels in the population of women of childbearing age in NYC?
8. What are the determinants blood lead concentrations in pregnant women?
9. What are the indications for chelation in pregnant women with elevated blood lead concentrations?
10. What is the clinic impact on lead levels of nutritional interventions?

A search of medical databases was conducted which included Medline and Cochrane Reviews for:

- Pregnancy and lead poisoning
- Pregnancy and lead intoxication
- Pregnancy and chelation
- Prevalence and pregnancy and lead
- Pregnancy and calcium and lead
- Pregnancy and chelation and lead
- Pica and pregnancy and lead
- Pregnancy and lead exposure
- Calcium supplementation and lead poisoning
- Pica and pregnancy
- Pregnancy and lead and outcome
- Pregnancy and lead and guidelines
- Pregnancy and lead and screening
- Mexico City Prospective Lead Study
- Lead Poisoning and Education
- Lead Poisoning and Nutrition
- Pregnancy and lead

Of those articles:

- Pubmed search for primary author of all articles
- Reviewed bibliographies of all articles retrieved and added relevant articles
- Pubmed "related links" for most relevant articles
- Exclusion Criterion:
  - Non-English language
  - Non-human subjects

Initially, the Authors, titles and sources were recorded in an Excel database for the relevant articles. They were organized by categories similar to expert panel tasks and listed in alphabetical order by first author. The abstracts were printed and reviewed with elimination of articles that contained content that was not relevant to our project.
The literature search included contacting offices of public health in states of similar size and demographics to obtain their current approaches to primary and secondary prevention of lead poisoning in pregnant women.

At a later point in the project, all of the data was switched to a RefWorks® database. Each of the abstracts retrieved were reviewed for relevancy and studies were eliminated by the following exclusion criteria:

- Not an Original article or not a Meta-Analysis or not a Systematic Review
- Animal Studies (except where the only data is from animal research)
- Not done on Pregnant women (not strictly upheld, much data is available and relevant from studies done on other populations)
- Non-English language (except if already translated)
- Did not use actual lead measurement to detect exposure
- Irrelevant

Each of the remaining articles were then retrieved and reviewed for the same exclusion criteria. For epidemiological studies, the most recent studies were used. Studies were screened for presentation of the data and results from the same study and the most comprehensive article was used.

The initial search yielded over 1000 articles. These were eliminated by title. After assessment of abstracts, there remained approximately 250 articles. Of the 250 articles, many turned out to be general review articles, letters to the editors or irrelevant, outdated or pilot studies of work published at a later date.

The next step in the process was to assess the quality of each of the studies. We devised a method which attempts to quantify the quality of the article from the viewpoint of Evidence Based Medicine. A list of well accepted quality measures were taken from table 1 of the article listed below{{171 Balk,E.M. 2002; }}. The modified version is:

Did the authors define the question in the introduction or methods? (yes/no)
If not, was the question defined anywhere? (yes/no)
Was there a placebo control or a Control group or none?
Were study outcomes appropriate based on study design, condition and intervention studied? (yes/no)
Were inclusion and exclusion criteria clearly and completely reported? (yes/no)
For Randomized Control trials:
- Were the randomization methods described?(yes/no/NA)
- Was the randomization site central, local or not described?(central/local/not described/NA)
- Was the allocation fully concealed?(yes/no/NA)
- Were the Patients/Subjects blinded?(yes/no/NA)
- Were the caregiver blinded?(yes/no/NA)
- Were the outcome assessors blinded?(yes/no/NA)
- Were the data analysts blinded?(yes/no/NA)
Was this a double blinded study? (yes/no/NA)
Were the statistical methods used valid? (yes/no)
Was a statistician one of the authors or acknowledged in the article? (yes/no)
Were all the patients analyzed in the group to which they were originally allocated? (yes/no/NA)
Was a power calculation reported? (yes/no/NA)
Were stopping rules described? (yes/no/NA)
Were baseline characteristics reported? (yes/no)
Were the groups similar at baseline? (yes/no)
Were confounders accounted for? (yes/no)
Were the number of dropouts recorded? (yes/no)
What percentage of subjects dropped out?
Were the reasons for dropouts reported? (yes/no)
Did the findings support the conclusions? (yes/no)

The articles are being reviewed by a diverse group with different levels of experience. Therefore, we made the criteria for each response as straightforward as possible. The statistic were valid if they used the appropriate test for the most complex variable. The study used a statistician if a person with an MPH or PhD was an author or acknowledged.

Each of the outcome responses was defined a value of 0 or 1. The total number of positive answers (i.e. yes, dropout rate <15%, etc…) were added together and then subtracted by the total number of applicable questions. The quality was defined as ≤0.6 = Low, 0.6-0.8 = Medium, ≥0.8 = High. As the denominator is not constant, this value is a rough estimate of the quality. When the articles were evaluated by the reviewers, the general consensus was that the quality measures were consistent with our general assessment. These measures were used to weight the conclusions of the study and to help us eliminate articles that we were unsure if they should be included. Many articles of low quality were retained because they provided either factual information or the study was unique to the question being asked.

The reviewers were responsible for the quality assessment, summary and critical review. The reviewers were referred to the website of the Canadian Center for Health Evidence. The site outlines the user’s guide to the medical literature and provide a framework for the critical review. In order to help with the assessment of the studies, we looked at the study type to decide if it was appropriately used for the outcome measured. The definitions were standardized as follows:

**Case-Control Study:**
A study designed to determine the association between an exposure and outcome in which patients are sampled by outcome (that is, some patients with the outcome of interest are selected, and compared to a group of patients who have not had the outcome) and the investigator examines the proportion of patients with the exposure in the two groups. (Retrospective)
Case Reports:
Descriptions of individual patients.

Cohort Study (or Cohort Analytic Study):
Prospective investigation of the factors that might cause a disorder in which a cohort of individuals who do not have evidence of an outcome of interest but who are exposed to the putative cause are compared with a concurrent cohort who are also free of the outcome but not exposed to the putative cause. Both cohorts are then followed to compare the incidence of the outcome of interest.

Synonymous with Prospective Study, Longitudinal Study

Controlled Trial:
Experiment in which individuals are randomly allocated to receive or not receive an experimental preventative, therapeutic or diagnostic procedure and then followed to determine the effect of the intervention.

Synonymous with Randomized Trial.

Cross-Sectional Survey:
The observation of a defined population at a single point in time or during a specific time interval. Exposure and outcome are determined simultaneously.

Meta-Analysis:
An overview that incorporates a quantitative strategy for combining the results of several studies into a single pooled or summary estimate.

Non-randomized Control:
Experiment in which assignment of patients to the intervention groups is at the convenience of the investigator or according to a preset plan that does not conform to the definition of random.

Observational Studies (or Observational Study Design):
Studies in which patient or physician preference determines whether a patient receives treatment or control.

Prognostic Study:
A study that enrolls patients at a point in time and follows them forward to determine the frequency and timing of subsequent events.

Randomized Controlled Trial:
Experiment in which individuals are randomly allocated to receive or not receive an experimental preventative, therapeutic or diagnostic procedure and then followed to determine the effect of the intervention.

Synonymous with Randomized Trial.
**Survey:**
Observational or descriptive non-experimental study in which individuals are systematically examined for the absence or presence (or degree of presence) of characteristics of interest.

**Systematic Review:**
A critical assessment and evaluation of research (not simply a summary) that attempts to address a focused clinical question using methods designed to reduce the likelihood of bias.

Source: Users’ Guides to the Medical Literature: A Manual for Evidence Based Clinical Practice

The results were entered into the RefWorks® database. The abstracts were standardized to include a minimum of 4 sections, the purpose or objective, methods, results and conclusions. These were expanded upon after reading the article. The next section is the quality measure. The study population was highlighted and the outcomes assessed were entered next. The final section of the output format are the comment and criticism section. This includes major points, unless already implicitly stated in the abstract, and the limitations of the study.

From the RefWorks® database, we will print out and distribute a synopsis book of the relevant studies. These will be distributed to each of the panel participants for review. We will ask each of the panelist to consider the evidence for each of the clinical questions. At this point, additional references will be added as per the panelists suggestions. The complete review will be summarized and the evidence discussed at the panel meetings. This will be used to make decisions regarding the charge questions and guideline modifications. Through the above outlined methods, we hope to reduce bias to a minimum and provide the best possible evidence regarding lead poisoning in pregnant women.