Chapter Two References

1. **Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term**

Abstract

"BACKGROUND:

The rate of elective primary cesarean delivery continues to rise, owing in part to the widespread perception that the procedure is of little or no risk to healthy women.

METHODS:

Using the Canadian Institute for Health Information's Discharge Abstract Database, we carried out a retrospective population-based cohort study of all women in Canada (excluding Quebec and Manitoba) who delivered from April 1991 through March 2005. Healthy women who underwent a primary cesarean delivery for breech presentation constituted a surrogate "planned cesarean group" considered to have undergone low-risk elective cesarean delivery, for comparison with an otherwise similar group of women who had planned to deliver vaginally.

RESULTS:

The planned cesarean group comprised 46,766 women v. 2,292,420 in the planned vaginal delivery group; overall rates of severe morbidity for the entire 14-year period were 27.3 and 9.0, respectively, per 1000 deliveries. The planned cesarean group had increased postpartum risks of cardiac arrest (adjusted odds ratio [OR] 5.1, 95% confidence interval [CI] 4.1-6.3), wound hematoma (OR 5.1, 95% CI 4.6-5.5), hysterectomy (OR 3.2, 95% CI 2.2-4.8), major puerperal infection (OR 3.0, 95% CI 2.7-3.4), anesthetic complications (OR 2.3, 95% CI 2.0-2.6), venous thromboembolism (OR 2.2, 95% CI 1.5-3.2) and hemorrhage requiring hysterectomy (OR 2.1, 95% CI 1.2-3.8), and stayed in hospital longer (adjusted mean difference 1.47 d, 95% CI 1.46-1.49 d) than those in the planned vaginal delivery group, but a lower risk of hemorrhage requiring blood transfusion (OR 0.4, 95% CI 0.2-0.8). Absolute risk increases in severe maternal morbidity rates were low (e.g., for postpartum cardiac arrest, the increase with planned cesarean delivery was 1.6 per 1000 deliveries, 95% CI 1.2-2.1). The difference in the rate of in-hospital maternal death between the 2 groups was nonsignificant ($p = 0.87$).

INTERPRETATION:

Although the absolute difference is small, the risks of severe maternal morbidity associated with planned cesarean delivery are higher than those associated with planned vaginal delivery. These risks should be considered by women contemplating an elective cesarean delivery and by their physicians."

Link:
http://www.ncbi.nlm.nih.gov/pubmed/17296957

Reference:

Liu, S., R. M. Liston, K.s. Joseph, M. Heaman, R. Sauve, and M. S. Kramer. "Maternal Mortality and Severe Morbidity Associated with Low-risk Planned Cesarean Delivery versus Planned Vaginal Delivery at Term." Canadian Medical Association Journal 176.4 (2007): 455-60.

2. **Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of mtDNA**

Abstract

"Thimerosal generates ethylmercury in aqueous solution and is widely used as preservative. We have investigated the toxicology of Thimerosal in normal human astrocytes, paying particular attention to mitochondrial function and the generation of specific oxidants. We find that ethylmercury not only inhibits mitochondrial respiration leading to a drop in the steady state membrane potential, but also concurrent with these phenomena increases the formation of superoxide, hydrogen peroxide, and Fenton/Haber-Weiss generated hydroxyl radical. These oxidants increase the levels of cellular aldehyde/ketones. Additionally, we find a five-fold increase in the levels of oxidant damaged mitochondrial DNA bases and increases in the levels of mtDNA nicks and blunt-ended breaks. Highly damaged mitochondria are characterized by having very low membrane potentials, increased superoxide/hydrogen peroxide production, and extensively damaged mtDNA and proteins. These mitochondria appear to have undergone a permeability transition, an observation supported by the five-fold increase in Caspase-3 activity observed after Thimerosal treatment."

Link:
http://www.ncbi.nlm.nih.gov/pubmed/23482308

Reference:

Sharpe, Martyn A., Andrew D. Livingston, and David S. Baskin. "Thimerosal-Derived Ethylmercury Is a Mitochondrial Toxin in Human Astrocytes: Possible Role of Fenton Chemistry in the Oxidation and Breakage of MtDNA." Journal of Toxicology 2012 (2012): 1-12.

3. **Is 5-methyltetrahydrofolate an alternative to folic acid for the prevention of neural tube defects?**

Abstract

"Women have higher requirements for folate during pregnancy. An optimal folate status must be achieved before conception and in the first trimester when the neural tube closes. Low maternal folate status is causally related to neural tube defects (NTDs). Many NTDs can be prevented by increasing maternal folate intake in the preconceptional period. Dietary folate is protective, but recommending increasing folate intake is ineffective on a population level particularly during periods of high demands. This is because the recommendations are often not followed or because the bioavailability of food folate is variable. Supplemental

folate [folic acid (FA) or 5-methyltetrahydrofolate (5-methylTHF)] can effectively increase folate concentrations to the level that is considered to be protective. FA is a synthetic compound that has no biological functions unless it is reduced to dihydrofolate and tetrahydrofolate. Unmetabolized FA appears in the circulation at doses of >200 μg. Individuals show wide variations in their ability to reduce FA. Carriers of certain polymorphisms in genes related to folate metabolism or absorption can better benefit from 5-methylTHF instead of FA. 5-MethylTHF [also known as (6S)-5-methylTHF] is the predominant natural form that is readily available for transport and metabolism. In contrast to FA, 5-methylTHF has no tolerable upper intake level and does not mask vitamin B12 deficiency. Supplementation of the natural form, 5-methylTHF, is a better alternative to supplementation of FA, especially in countries not applying a fortification program. Supplemental 5-methylTHF can effectively improve folate biomarkers in young women in early pregnancy in order to prevent NTDs."

Link:

http://www.ncbi.nlm.nih.gov/pubmed/23482308

Reference:

Obeid, Rima, Wolfgang Holzgreve, and Klaus Pietrzik. "Is 5-methyltetrahydrofolate an Alternative to Folic Acid for the Prevention of Neural Tube Defects?" Journal of Perinatal Medicine 41.5 (2013).

4. Inflammatory Responses to Trivalent Influenza Virus Vaccine Among Pregnant Women

Abstract

"**Objective**

In the U.S., seasonal trivalent influenza vaccination (TIV) is currently universally recommended for all pregnant women. However, data on the maternal inflammatory response to vaccination is lacking and would better delineate the safety and clinical utility of immunization. In addition, for research purposes, vaccination has been used as a mild immune trigger to examine *in vivo* inflammatory responses in nonpregnant adults. The utility of such a model in pregnancy is unknown. Given the clinical and empirical justifications, the current study examined the magnitude, time course, and variance in inflammatory responses following seasonal influenza virus vaccination among pregnant women.

Methods

Women were assessed prior to and at one day (n=15), two days (n=10), or approximately one week (n=21) following TIV. Serum interleukin (IL)-6, tumor necrosis factor (TNF)-α, C-reactive

protein (CRP), and macrophage migration inhibitory factor (MIF) were determined by high sensitivity immunoassay.

Results

Significant increases in CRP were seen at one and two days post-vaccination (*p*s <.05). A similar effect was seen for TNF-α, for which an increase at two days post-vaccination approached statistical significance ($p = .06$). There was considerable variability in magnitude of response; coefficients of variation for change at two days post-vaccination ranged from 122% to 728%, with the greatest variability in IL-6 responses at this timepoint.

Conclusions

Trivalent influenza virus vaccination elicits a measurable inflammatory response among pregnant women. There is sufficient variability in response for testing associations with clinical outcomes. As adverse perinatal health outcomes including preeclampsia and preterm birth have an inflammatory component, a tendency toward greater inflammatory responding to immune triggers may predict risk of adverse outcomes, providing insight into biological mechanisms underlying risk. The inflammatory response elicited by vaccination is substantially milder and more transient than seen in infectious illness, arguing for the clinical value of vaccination. However, further research is needed to confirm that the mild inflammatory response elicited by vaccination is benign in pregnancy."

Link:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3204610/

Reference:

Christian, Lisa M., Jay D. Iams, Kyle Porter, and Ronald Glaser. "Inflammatory Responses to Trivalent Influenza Virus Vaccine among Pregnant Women." Vaccine 29.48 (2011): 8982-987.

5. High concentrations of folate and unmetabolized folic acid in a cohort of pregnant Canadian women and umbilical cord blood

Abstract

"**Background:**

Mandatory fortification, prevalent supplement use, and public health guidelines recommending periconceptional supplementation have increased folic acid intakes in North American pregnant women. However, the effects of increased folic acid intakes during pregnancy on maternal and cord blood folate concentrations have not been well established.

Objectives:

In this prospective study, we determined maternal and cord blood concentrations of folate and unmetabolized folic acid (UMFA) in a cohort of pregnant Canadian women and their newborns and examined the effect of maternal intakes of folate and folic acid and fetal genetic variants in folate metabolism on folate status.

Design:

Folate and folic acid intakes of 368 Canadian pregnant women were assessed in early (0–16 wk) and late (23–37 wk) pregnancy. Blood concentrations of folate and UMFA were measured with the use of immunoassays and liquid chromatography–mass spectrometry, respectively, in maternal samples in early pregnancy (12–16 wk), at delivery (28–42 wk), and in cord blood. Four fetal genetic variants of the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) and dihydrofolate reductase (*DHFR*) genes were assessed for their association with cord blood concentrations of folate and UMFA.

Results:

Geometric mean (95% CI) maternal red blood cell (RBC) folate concentrations were 2417 nmol/L (2362, 2472 nmol/L) and 2793 nmol/L (2721, 2867 nmol/L) in early pregnancy and at delivery, respectively. The mean (95% CI) cord RBC folate concentration was 2689 nmol/L (2614, 2765 nmol/L). UMFA was detectable in >90% of maternal and cord plasma samples. Although 3 fetal *MTHFR*and *DHFR* genetic variants had no effect, the fetal *MTHFR* 677TT genotype was associated with significantly lower cord serum ($P = 0.03$) and higher cord RBC ($P = 0.02$) folate concentrations than those of the wild type.

Conclusions:

Notwithstanding differences in assays, maternal and cord RBC folate and plasma UMFA concentrations were higher than previously reported values. Functional ramifications of high folate and UMFA concentrations in maternal and fetal circulation warrant additional investigation because an excess folate status may affect long-term health outcomes of the offspring. ”

Link:

http://ajcn.nutrition.org/content/early/2015/08/12/ajcn.115.110783

Reference:

Plumptre, L., S. P. Masih, A. Ly, S. Aufreiter, K.-J. Sohn, R. Croxford, A. Y. Lausman, H. Berger, D. L. O'connor, and Y.-I. Kim. "High Concentrations of Folate and Unmetabolized Folic Acid in a Cohort of Pregnant Canadian Women and Umbilical Cord Blood." American Journal of Clinical Nutrition 102.4 (2015): 848-57.\

6. Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy: cohort study

Abstract

"**Objective**

To assess the risk of maternal, fetal, and neonatal outcomes associated with the administration of an MF59 adjuvanted A/H1N1 vaccine during pregnancy.

Design

Historical cohort study.

Setting

Singleton pregnancies of the resident population of the Lombardy region of Italy.

Participants

All deliveries between 1 October 2009 and 30 September 2010. Data on exposure to A/H1N1 pandemic vaccine, pregnancy, and birth outcomes were retrieved from regional databases. Vaccinated and non-vaccinated women were compared in a propensity score matched analysis to estimate risks of adverse outcomes.

Main outcome measures

Main maternal outcomes included type of delivery, admission to intensive care unit, eclampsia, and gestational diabetes; fetal and neonatal outcomes included perinatal deaths, small for gestational age births, and congenital malformations.

Results

Among the 86 171 eligible pregnancies, 6246 women were vaccinated (3615 (57.9%) in the third trimester and 2557 (40.9%) in the second trimester). No difference was observed in terms of spontaneous deliveries (adjusted odds ratio 1.02, 95% confidence interval 0.96 to 1.08) or admissions to intensive care units (0.95, 0.47 to 1.88), whereas a limited increase in the prevalence of gestational diabetes (1.26, 1.04 to 1.53) and eclampsia (1.19, 1.04 to 1.39) was seen in vaccinated women. Rates of fetal and neonatal outcomes were similar in vaccinated and non-vaccinated women. A slight increase in congenital malformations, although not statistically significant, was present in the exposed cohort (1.14, 0.99 to 1.31).

Conclusions

Our findings add relevant information about the safety of the MF59 adjuvanted A/H1N1 vaccine in pregnancy. Residual confounding may partly explain the increased risk of some maternal outcomes. Meta-analysis of published studies should be conducted to further clarify the risk of infrequent outcomes, such as specific congenital malformations."

Link:
http://www.bmj.com/content/348/bmj.g3361
Reference:

Trotta, F., R. Da Cas, S. Spila Alegiani, M. Gramegna, M. Venegoni, C. Zocchetti, and G. Traversa. "Evaluation of Safety of A/H1N1 Pandemic Vaccination during Pregnancy: Cohort Study." BMJ 348.May29 5 (2014).

7. Enhanced natural killer-cell and T-cell responses to influenza A virus during pregnancy

Abstract

"Pregnant women experience increased morbidity and mortality after influenza infection, for reasons that are not understood. Although some data suggest that natural killer (NK)- and T-cell responses are suppressed during pregnancy, influenza-specific responses have not been previously evaluated. Thus, we analyzed the responses of women that were pregnant (n = 21) versus those that were not (n = 29) immediately before inactivated influenza vaccination (IIV), 7 d after vaccination, and 6 wk postpartum. Expression of CD107a (a marker of cytolysis) and production of IFN-γ and macrophage inflammatory protein (MIP) 1β were assessed by flow cytometry. Pregnant women had a significantly increased percentage of NK cells producing a MIP-1β response to pH1N1 virus compared with nonpregnant women pre-IIV [median, 6.66 vs. 0.90% (P = 0.0149)] and 7 d post-IIV [median, 11.23 vs. 2.81% (P = 0.004)], indicating a heightened chemokine response in pregnant women that was further enhanced by the vaccination. Pregnant women also exhibited significantly increased T-cell production of MIP-1β and polyfunctionality in NK and T cells to pH1N1 virus pre- and post-IIV. NK- and T-cell polyfunctionality was also enhanced in pregnant women in response to the H3N2 viral strain. In contrast, pregnant women had significantly reduced NK- and T-cell responses to phorbol 12-myristate 13-acetate and ionomycin. This type of stimulation led to the conclusion that NK- and T-cell responses during pregnancy are suppressed, but clearly this conclusion is not correct relative to the more biologically relevant assays described here. Robust cellular immune responses to influenza during pregnancy could drive pulmonary inflammation, explaining increased morbidity and mortality."

Link:
http://www.pnas.org/content/111/40/14506.abstract
Reference:

Trotta, F., R. Da Cas, S. Spila Alegiani, M. Gramegna, M. Venegoni, C. Zocchetti, and G. Kay, Alexander W., Julia Fukuyama, Natali Aziz, Cornelia L. Dekker, Sally Mackey, Gary E. Swan, Mark M. Davis, Susan Holmes, and Catherine A. Blish. "Enhanced Natural Killer-cell and T-cell Responses to Influenza A Virus during Pregnancy." Proceedings of the National Academy of Sciences Proc Natl Acad Sci USA 111.40 (2014): 14506-4511.

8. **Enhanced natural killer-cell and T-cell responses to influenza A virus during pregnancy**

Abstract

"Pregnant women experience increased morbidity and mortality after influenza infection, for reasons that are not understood. Although some data suggest that natural killer (NK)- and T-cell responses are suppressed during pregnancy, influenza-specific responses have not been previously evaluated. Thus, we analyzed the responses of women that were pregnant (n = 21) versus those that were not (n = 29) immediately before inactivated influenza vaccination (IIV), 7 d after vaccination, and 6 wk postpartum. Expression of CD107a (a marker of cytolysis) and production of IFN-γ and macrophage inflammatory protein (MIP) 1β were assessed by flow cytometry. Pregnant women had a significantly increased percentage of NK cells producing a MIP-1β response to pH1N1 virus compared with nonpregnant women pre-IIV [median, 6.66 vs. 0.90% (P = 0.0149)] and 7 d post-IIV [median, 11.23 vs. 2.81% (P = 0.004)], indicating a heightened chemokine response in pregnant women that was further enhanced by the vaccination. Pregnant women also exhibited significantly increased T-cell production of MIP-1β and polyfunctionality in NK and T cells to pH1N1 virus pre- and post-IIV. NK- and T-cell polyfunctionality was also enhanced in pregnant women in response to the H3N2 viral strain. In contrast, pregnant women had significantly reduced NK- and T-cell responses to phorbol 12-myristate 13-acetate and ionomycin. This type of stimulation led to the conclusion that NK- and T-cell responses during pregnancy are suppressed, but clearly this conclusion is not correct relative to the more biologically relevant assays described here. Robust cellular immune responses to influenza during pregnancy could drive pulmonary inflammation, explaining increased morbidity and mortality."

Link:
http://www.pnas.org/content/111/40/14506.abstract

Reference:

Trotta, F., R. Da Cas, S. Spila Alegiani, M. Gramegna, M. Venegoni, C. Zocchetti, and G. Kay, Alexander W., Julia Fukuyama, Natali Aziz, Cornelia L. Dekker, Sally Mackey, Gary E. Swan, Mark M. Davis, Susan Holmes, and Catherine A. Blish. "Enhanced Natural Killer-cell and T-cell Responses to Influenza A Virus during Pregnancy." Proceedings of the National Academy of Sciences Proc Natl Acad Sci USA 111.40 (2014): 14506-4511.

9. **Elevated maternal C-reactive protein and autism in a national birth cohort.**

Abstract

"Autism is a complex neuropsychiatric syndrome with a largely unknown etiology. Inflammation during pregnancy may represent a common pathway by which infections and other insults increase risk for the disorder. Hence, we investigated the association between early gestational C-reactive protein (CRP), an established inflammatory biomarker, prospectively assayed in maternal sera, and childhood autism in a large national birth cohort

with an extensive serum biobank. Other strengths of the cohort included nearly complete ascertainment of pregnancies in Finland (N=1.2 million) over the study period and national psychiatric registries consisting of virtually all treated autism cases in the population. Increasing maternal CRP levels, classified as a continuous variable, were significantly associated with autism in offspring. For maternal CRP levels in the highest quintile, compared with the lowest quintile, there was a significant, 43% elevated risk. This finding suggests that maternal inflammation may have a significant role in autism, with possible implications for identifying preventive strategies and pathogenic mechanisms in autism and other neurodevelopmental disorders."

Link

http://www.ncbi.nlm.nih.gov/pubmed/23337946

References

Brown, A. S., A. Sourander, S. Hinkka-Yli-Salomäki, I. W. Mckeague, J. Sundvall, and H-M Surcel. "Elevated Maternal C-reactive Protein and Autism in a National Birth Cohort." Molecular Psychiatry Mol Psychiatry 19.2 (2013): 259-64.

10. Depressive symptoms are associated with elevated serum proinflammatory cytokines among pregnant women.

Abstract

"Psychosocial stress and depressive symptoms are associated with increased risk of negative perinatal outcomes including preterm delivery and gestational hypertension. Inflammation is a likely mechanism by which distress may promote these outcomes. It is well-established that stress and depressive symptoms are associated with elevated serum inflammatory markers in nonpregnant populations. However, the immune system exhibits significant changes during pregnancy. Thus, the extent to which these findings extend to pregnancy is largely unknown. The current study examined associations among perceived stress, depressive symptoms, and serum inflammatory markers in a sample of 60 pregnant women. Fifty seven percent were African-American, 82% had completed high school or less education, and 63% reported an annual family income below $15,000. Participants completed the Perceived Stress Scale (PSS) and the Center for Epidemiologic Studies Depression Scale (CES-D). Serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) were determined using high sensitivity immunoassays. Regression analyses demonstrated that after controlling for pre-pregnancy Body Mass Index (BMI), higher scores on the CES-D were related to significantly higher levels of IL-6 (beta=.23, p=.05) and marginally higher TNF-alpha (beta=.24, p=.06). Perceived stress was not significantly related to serum levels of IL-6 or TNF-alpha. In sum, these results indicate that depressive symptoms are associated with higher levels of maternal serum inflammatory markers during pregnancy. These data are consistent with the contention that depressive symptoms may contribute to negative perinatal outcomes via inflammatory pathways.'

Link:

http://www.ncbi.nlm.nih.gov/pubmed/19258033

Reference:

Christian, Lisa M., Albert Franco, Ronald Glaser, and Jay D. Iams. "Depressive Symptoms Are Associated with Elevated Serum Proinflammatory Cytokines among Pregnant Women." Brain, Behavior, and Immunity 23.6 (2009): 750-54.

11. Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) Databases

Abstract

"**IMPORTANCE:**

One in 88 children in the United States is diagnosed as having autism spectrum disorder. Significant interest centers on understanding the environmental factors that may contribute to autism risk.

OBJECTIVE:

To examine whether induced (stimulating uterine contractions prior to the onset of spontaneous labor) and/or augmented (increasing the strength, duration, or frequency of uterine contractions with spontaneous onset of labor) births are associated with increased odds of autism.

DESIGN, SETTING, AND PARTICIPANTS:

We performed an epidemiological analysis using multivariable logistic regression modeling involving the North Carolina Detailed Birth Record and Education Research databases. The study featured 625,042 live births linked with school records, including more than 5500 children with a documented exceptionality designation for autism.

EXPOSURES:

Induced or augmented births.

MAIN OUTCOMES AND MEASURES:

Autism as assessed by exceptionality designations in child educational records.

RESULTS:

Compared with children born to mothers who received neither labor induction nor augmentation, children born to mothers who were induced and augmented, induced only, or augmented only experienced increased odds of autism after controlling for potential confounders related to socioeconomic status, maternal health, pregnancy-related events and conditions, and birth year. The observed associations between labor induction/augmentation were particularly pronounced in male children.

CONCLUSIONS AND RELEVANCE:

Our work suggests that induction/augmentation during childbirth is associated with increased odds of autism diagnosis in childhood. While these results are interesting, further investigation is needed to differentiate among potential explanations of the association including underlying pregnancy conditions requiring the eventual need to induce/augment, the events of labor and delivery associated with induction/augmentation, and the specific treatments and dosing used to induce/augment labor (e.g., exogenous oxytocin and prostaglandins).

Links:

http://www.ncbi.nlm.nih.gov/pubmed/23938610

References:

Gregory, Simon G., Rebecca Anthopolos, Claire E. Osgood, Chad A. Grotegut, and Marie Lynn Miranda. "Association of Autism With Induced or Augmented Childbirth in North Carolina Birth Record (1990–1998) and Education Research (1997–2007) Databases." Obstetrical & Gynecological Survey 69.1 (2014): 7-9.

12. All that palsies is not Bell's -the need to define Bell's palsy as an adverse event following immunization.

Abstract

“Bell's palsy has been reported as an adverse event following immunization (AEFI). Review of the published literature reveals that several characteristics have been used to describe Bell's palsy, which differ significantly from author to author. Evidently, the definition of "Bell's palsy" remains controversial, and consensus between different medical subspecialties is urgently needed. The Brighton Collaboration has formed an international working group with representatives of neurology, otorhinolaryngology, pediatrics, electrophysiology, pharmacology, pharmaceutical and biotech industry as well as regulatory agencies to create a case definition of Bell's palsy as an AEFI.”

Links

http://www.ncbi.nlm.nih.gov/pubmed/18037542

Reference

Rath, Barbara, Thomas Linder, David Cornblath, Michael Hudson, Rohini Fernandopulle, Katharina Hartmann, Ulrich Heininger, Hector Izurieta, Leslie Killion, Pangiotis Kokotis, James Oleske, Michael Vajdy, and Virginia Wong. "“All That Palsies Is Not Bell's [1]”—The Need to Define Bell's Palsy as an Adverse Event following Immunization." Vaccine 26.1 (2007): 1-14.