

# Perinatal Medicine: Research Review

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# Outline

- Vitamin D
- Celiac Disease
- Inflammatory Breast Cancer
- Probiotics
- Gestational Diabetes
- Folic Acid
- Mental/Emotional Performance
- Autism
- Zika and More

# Vitamin D

## Respiratory Infections (ARI) Meta-analysis B j Nutr.2015;114:1026-1034.

- ARI---11.9x10<sup>6</sup> 2010, 3x10<sup>6</sup> hospitalized, 2/3 of 7.6x10<sup>6</sup> deaths to age 5 are infections; Pneumonia 1.396x10<sup>6</sup>
- Search to March 2014
- Criteria---
  - RCT
  - dosage, mode, duration
  - defined ARI
  - Prevalence, relative risk, confidence intervals
  - < 18 yo

- Findings---
  - 1329 references
  - 68 articles reviewed
  - 7 included
- Outcomes
  - Sig—def vit D and susceptibility to ARI
  - NS---Bolus doses reported no effect or immunosuppressive effect (e.g. 100,000 IU/d)
  - Sig---daily dose schedule
  - Vit D---decr growth of airway smooth muscles stimulated by platelet-derived growth factor

- Outcomes---

- Asthma—vit D reduces exacerbations by respiratory infection, 74% reduction
- Pneumonia—linear relationship btwn D status and illness frequency
- D status should be tested before administration in clinical trials
- Avoid supra physiological doses of D, i.e. dose daily with foods containing fats/oils

# Celiac Disease

## Breastfeeding and Celiac Disease Review

BMJ.2016;6(1):e009163.

- N=149 papers, 48 reviewed in depth, 16 included
- Outcomes re: Prevention of Celiac
  - NS---duration of breastfeeding
  - NS---breast fed or not breast fed
  - NS---breast fed when gluten introduced
  - NS---gluten during weaning

# Inflammatory Breast Cancer

## Inflammatory Brst CA (IBC) Risks Cancer Causes Control.2016;Jan21.Epub.

- MD Anderson case-control study
- N=224 IBC
- N=396 cancer-free
- Outcomes---
  - < 26 yo first pregnancy higher risk, OR 3.32, triple-negative compared to  $\geq$  26 yo first pregnancy
  - Breast-feeding lower risk triple-negative
  - Breast-feeding lower risk luminal IBC

- Outcomes
  - History smoking---incr risk luminal brst CA, OR 2.37
  - Over weight/obese---BMI  $\geq 25$  kg/m<sup>2</sup> higher risk of a breast cancer types,  $p < 0.01$
- Conclusions---
  - Breast feed
  - Stop smoking
  - Control weight



# Probiotics

## Probiotics and Gestational Diabetes (GDM) J health Popul

Nutr.2015;33(10:25doi10.186.

- N=64 GDM
- Tx---probiotic vs placebo; all diet advice; DB, PC, Ran; 8 wk
- Outcomes---
  - NS---wt gain to 6 wk
  - Sig---wt gain at 8 wk, lower Tx,  $p<0.05$
  - Sig---fasting glucose decr
    - 103.7 → 88.4 probiotic
    - 100.9 → 93.6 placebo; Tx Sig vs Placebo

- Outcomes---

- Insulin resistance index--NS

- Probiotic decr 6.74%,  $p < 0.05$
    - Placebo incr 6.45%

- Insulin sensitivity index

- Incr Probiotic, not Sig from baseline
    - Incr Placebo, not Sig from baseline

# Gestational Diabetes

## Body composition and gestational diabetes (GDM)

Biomed Environ sci.2016;29(1):1-11.

- N=11 hospitals China; May 2012-Dec 2103
- N=154 GDM, N=981 controls
- Measure
  - Wk 21-24 gestation
  - Bioelectrical impedance analysis
  - Diet survey

- Risk Factors
  - Older age
  - Pre-pregnant body wt
  - BMI
- Additional Risks
  - Fat mass
  - % fat mass
  - Extracellular water
  - Higher intake—Energy, Protein, Fat, Carb wk 21-24

- Risk Reduction
  - Free fat mass
  - Muscular mass
  - Intracellular water

## Non-alcohol Fatty Liver (NAFLV) and GDM (gestational diabetes mellitus) Am J Gastgro.2016.doi.10.1038.

- N=476, OB clinic Toronto, Ontario
- US Dx for NAFLV at 11-14 wk gestation
- Maternal age, ethnicity, relatives w/ T2D, BMI at 11-14 wk gestation, BMI at 24-28 wk gestation
- Oral glucose tolerance test---75g at 24-28 wk
- 50 of 476 developed GDM (OR 2.2-2.9, CI 1.1-4.3)
- US Dx NAFLV predicts GDM

## GDM and vit D

Arch Gynecol Obstet.2016.Epub.

- Search data bases to Jan 2015
- N=20 observational studies
- N=16,515 pregnant, DGM women
- Outcome
  - Vit D insufficiency associated w/ incr risk GDM, RR 1.45,  $p < 0.001$
  - Association may differ by country, age, study quality

# Obesity, Pregnancy and Metformin Trial

NEJM.2016;374(5):434-443.

- Pregnant w/o Diabetes & BMI >35, 2-18 wk gestation
- N=225 per group
- Tx---metformin 3g/d vs Placebo
- Outcomes
  - 50 withdrew → 202 metformin, 198 placebo



- Outcomes

- NS---neonatal birth weight
- Sig---maternal weight gain in Tx 4.6 kg vs 6.3 kg,  $p < 0.001$
- Sig---preeclampsia 3% Tx vs 11.3% placebo,  $p = 0.001$
- SE—greater in metformin vs placebo
- NS---gestational diabetes, large for gestational age neonates, adverse neonate outcomes

# Folic Acid

## Folic acid and asthma—TN Medicaid

Epidemiology.2015;26(6):934-941.

- N=104,428 children born 1996-2005
- Tx---filling folic acid prescriptions during pregnancy and asthma at 4.5-6 yo
  - Fill prescription
  - Trimester prescription filled
- Outcome
  - 15% Asthma by 4.5-6 yo

- Outcomes
  - 1<sup>st</sup> trimester only---incr asthma OR 1.2
  - 1<sup>st</sup> trimester and later---incr asthma OR 1.2
  - 2<sup>nd</sup> and 3<sup>rd</sup> trimester---no association seen
- Question---to folic acid or not?

## Folic acid, URI and Eczema Eur Respir J.2012;39(6):1468-1474.

- Prevention and incidence of asthma and mite allergy birth cohort, Netherlands
- N=3,786 children to age 8 yo
- Outcomes
  - NS---asthma Sx, wheeze 1-8 yo
  - NS---lower respiratory tract infections 1-8 yo

- Outcomes

- NS---frequency respiratory tract infections 1-8 yo
- NS---eczema 1-8 yo
- Sig---wheeze at 1 yo, OR 1.2, NOT at older age
- NS---bronchial hyper-responsiveness 1-8 yo
- NS---allergic sensitization 1-8 yo

## Asthma and Cesarean J Pediatr.2016;doi:10.1016.

- N=411 Danish Children, National Registry 1997-2010
- Asthma=recurrent use of inhaled corticosteroids filled at a pharmacy
- Cesarean either before or after rupture of membranes vs vaginal delivery
- Adjusted---age, calendar year, sex, birth weight, gestational age, multiple births, parity, maternal factors (smoking, antibiotic use, employment, status, asthma)

- Outcomes

- Asthma incr by cesarean vs vaginal birth, OR 2.18 (1.27-3.73)
- Cesarean deliver before membrane rupture incr risk of ashtma, OR 1.20 (1.1.6-1.23)
- Cesarean after membrane rupture incr risk of asthma OR 1.12 (1.09-1.16)

- Cesarean and Leukemia Lancet
- N=13 studies from Childhood Leukemia International Consortium
- N=33,571 children, N=8,665 acute lymphoblastic leukemia (ALL)
- Outcomes
  - 23% incr in ALL born through pre-labor cesarean



ALL Cancer.2014.64(2):83-103.

- #1 childhood cancer; 23-30% of cancer by 15 yo
  - #1 cause of child cancer death
  - 2-5 yo is peak; M>F (38.4-30.2), peak after 50 yo
  - Cure 80% children, 20-40% adults
- Tx---chemo, radiation, steroids, bone marrow transplant

# Leukemia and Prelabor Cesarean Delivery (CD)

Er J Cancer Prev.2016;25(2):155-161.

- N=1099 cases of AL (975 B-ALL)
- N=131 AML
- Controls---age, sex, Nationwide Registry for Childhood Malignancies 1996-2013, Greece
- Outcomes for CD
  - ALL odds ratio 1.57 (95% 1.10-2.24); if prelabor odds ratio 1.66 (95% 1.13-2.43)

- Outcomes
  - B-ALL odds ratio 1.66 (95% 1.15-2.40), if prelabor odds ratio 1.79 (95% 1.21-2.66)
  - AML no association
- Presumably labor exposes fetus to beneficial stress of hormones associated with vaginal labor and delivery
- Need to re-evaluate prelabor CD if confirmed

# Mental/Emotional Performance

## Protein Intake and Performance Br J Nutr.2016;22:1-9.epub.

- Human brain development maximum from 3<sup>rd</sup> trimester to 2 yo
- Protein recommendations for infancy childhood decreased---Question is safety? Consequences?
- EU CHOP Trial---Belgium, Germany, Italy, Poland, Spain
  - Less protein
  - Battery of tests
  - N=1678

- Protein Intake

- Breast fed---1-1.2 g/dL
- Conventional protein formula---2.05-3.2 g/dL
- Intervention formula 1.25-1.6 g/dl
- Limit to prevent cows milk

- Theory

- High protein → adult obesity
- High protein → ↑ IGF-1; Brst incr IGF-BP2

- Outcomes---NS
  - Memory—visual, working, verbal
  - Attention—visual, selective, focused, sustained
  - Visual—perceptual integration, spatial skills, motor coordination
  - Processing speed
  - Verbal—fluency, comprehension
  - Impulsivity/Inhibition
  - Flexibility/Shifting

- Outcomes---NS
  - Reasoning
  - Internalizing
  - Externalizing
  - Behavior problems
- Adjusted for---
  - Parental education
  - Maternal smoking
  - Mother's gestational age
  - Head circumference

## Maternal Stress Effects Peer J.2016;4:e1585.doi:10.7717.

- Psychological stress linked to atopy
- N=152 allergic children, X=13 mo old, no Sx in last 30 d, (Japan)
- Maternal Stress---
  - Centre for Epidemiological Studies Depression Scale (CESD)
  - Japanese Perceived Stress Scale JPSS
- Child Stress---
  - mRNA IL-6, IL-8, IL-10, IL-22, IgE in children



- Outcomes

- Sig---CESD and IL-6 in asthma
- Sig---JPSS and IL-8 in asthma
- Sig---JPSS and IL-6 in allergic rhinitis
- NS---JPSS and CESD and IgE for dust mites, but trend was positive

# Autism

## Autism and Brain Curr Biol.2016;26(1):80-85.

- Theory---prevalence of seizures suggests imbalanced excitatory/inhibitory neurotransmission
- Autopsy---fewer GABA receptor subunits
- Murine---GABAergic signaling disrupted
- MRI spectroscopy---link btwn GABA and binocular dynamics is absent in autism

# Oxytocin and neuropsychiatric disorders Front

Neurosci.2016;9:497.doi10.389.

- Oxytocin physiology---
  - oxytocin role in parturition
  - milk let-down
  - maternal behavior
  - mother-infant bonding
  - pair mating

- Oxytocin regulates---
  - social interaction
  - social memory response to social stimuli
  - social decision-making
  - feeding behavior
  - emotional reactivity
- De- or Dys-regulation in---
  - Autism
  - Eating disorders
  - Schizophrenia
  - Mood disorders
  - Anxiety disorders

## B vitamin Levels over Lifespan PLoS One.2016;11(1):e0146797.

- Methylcobalamin (MeB12) a cofactor for folate-dependent enzyme methionine synthetase (MS) and adenosylcobalamin a cofactor for methylmalonyl-CoA mutase (MCM)
- Study---levels of cobalamin species in frontal cortex postmortem
  - 43 control---from 19 week fetus to 80 yo
  - 12 autistic
  - 9 schizophrenic

- Outcomes---
  - Controls--MeB12 Sig lower > 60 yo; 10 fold age-dependent decline
  - Fetus---high inactive cyanoB12
  - Autistic---MeB12 and AdenB12 >3x lower than age-matched controls
  - Autistic---lower MeB12 associated w/ decr MS activity and elevated homocysteine
  - Schizophrenic---MeB12 and AdenB12 >3x lower than age-matched controls
  - Autistic, Schizophrenic---lower glutathione vs controls
- Autistic, Schizophrenic---need GSH, homocysteine support

# Autism and maternal supplementation Nutr

Neurosci.2015.27.epub.

- Theory---maternal infection, obesity, toxicant exposure disrupt early brain development → autism spectrum disorder (ASD) via maternal inflammatory response
- Results---maternal micronutrient supplementation is associated with reduced risk of ASD

# Autism and vitamin D systematic review Eur Child

Adolesc Psychiatry.2015;epub.

- N=11 trials
- N=870 patients, N=782 controls
- Outcomes
  - Sig---D lower in Autism vs Controls
- Other Risk Factors
  - D role in nerve myelination
  - Lower D during pregnancy, decr UVB



## D in Sibling Pairs

Mol Autism.2015;6:3 doi 10.1186/2040-2392-6-3.

- N=58 Swedish sibling pairs
  - 47---mixed ethnicity: Africa, Middle East
  - 11---Somali descent
  - 25 OH-D from dried blood spot in neonatal period
- Outcomes
  - Sig—lower D in Autism 24.0 nM vs 31.9 nM, p=0.013
  - Sig—all children had D deficiency

## Autism and Maternal Health

Autism Res.2016;doi.10.1002.epub.

- Cincinnati Children's Hospital and catchment
- Data Collection
  - Mother---
    - obesity,
    - gestational diabetes (GDM)
  - Child---
    - developmental disorder (DD)
    - autism spectrum disorder (ASD)

- Outcomes

- Obesity → ASD, 1.5x
- GDM → DD, 1.5x
- Obesity + GDM → 2.0x
- NS---ASD not linked more to obesity or ASD

## Polycystic ovary syndrome (PCOS) and autism spectrum disorder (ASD)

Mol Psychiatry.2015.doi:10.1038.epub.

- Matched case-control study of Swedish children born 1948-2007
- Matched by birth month, year, sex, region of birth
- Children---
  - 23,748 ASD
  - 208,796 controls

- Outcomes
  - PCOS → ASD by 59%, OR 1.59 (1.34-1.88)
  - PCOS + Obesity → OR 2.13 (1.46-3.10)
  - NS---risk by sex of child
- Question---role of androgens in etiology of ASD?

## Autism and Maternal Health Pediatrics.2016.peds2015-2206.epub.

- Boston Birth Cohort 1998-2014
  - Birth + one post-natal visit at Boston Medical Center
- Children
  - ASD---102
  - Normal---2634
- Mother---6 categories of pre-pregnancy obesity and diabetes and during pregnancy

- Outcomes

- Pre-pregnancy obesity → ASD
- Pre-gestational diabetes (PGDM) → ASD
- Obesity + Pre-gestational diabetes (hazard ratio 3.91 (1.76-8.68))
- Obesity + gestational diabetes hazard ratio 3.04 (1.21-7.63)
- Obesity + PGDM → intellectual disability (ID)  
(most were ASD + ID)

# Zika

- 1947 Uganda, Lake Victoria, captive rhesus monkey
- 1948 Tanzania, mosquito *Aedes africanus* in Zika Forest
- 1952 first human cases Uganda, Tanzania + antibodies in serum, 50 of 84 had antibodies & all immune
- 1952 study in India showed many had antibodies
- 1954 Nigeria, Cameroon



- 1975, 2007 Gabon
- 2007 Cabo Verde
- 2013/2014 French Polynesia, New Caledonia, Cook Islands, Easter Island
- 2015 Mexico, Central America, Caribbean, S America
- 2015-2016 Puerto Rico, US Virgin Islands

## Zika virus in Puerto Rico MMWR Morb Morb Wkly Rep.2016.65(6):154-158.

- Nov 23, 2015 – Jan 28, 2016
  - 30 lab dx cases
  - 93% eastern Puerto Rico, San Juan
  - *Aedes aegypti* throughout Puerto Rico
- Sx
  - Rash 77%
  - Myalgia 77%
  - Arthralgia 73%
  - Fever 73%
  - Hospitalized 10% (3)---1 Guillain-Barré, 1 pregnant female

- Related—Flavivirus ∴---dengue fever, yellow fever, Japanese encephalitis, west Nile virus, linked to Guillain-Barre Syn
- Lineage
  - African---89% of Western hemisphere
  - Asian—French Polynesia
  - Enzootic---mosquito-monkey-mosquito, occ human
- Vector---*Aedes aegypti* + *A. spp.*(6), 10 d incubation

- Vector---
  - *Aedes aegypti* + *A. spp.*(6), 10 d incubation
  - Found in *Anopheles coustani*, *Mansonia uniformis*, *Culex perfuscus* but a vector???
  - *A albopictus* (tiger mosquito) 2007 Gabon outbreak + dengue
- Sexual transmission---male to female
  - 3 known
  - 14 reported
  - Viable in semen 2-10 wk
- Blood donation---wait 28 d after sx abate (Canada)

- Infection Sx
  - HA, maculopapular rash, fever, malaise, conjunctivitis, point pain
  - No fatalities known
- Current Vaccines
  - Yellow fever, Japanese encephalitis, tick-borne encephalitis 1930s
  - Dengue fever 2010

## Zika and Gullian-Barré (GB) Lancet.2016.

- Incr Cases---Brazil, El Salvadorl Venequela
- French Polynesia 42 cases 201-2014
  - None died
  - 90% Zika-like Sx 4-10d before neurologic sx
  - 38% intensive care
  - 29% needed help breathing

- Zika effects
  - 74% had IgM against Zika, none against Dengue
  - All 42 formed antibodies=prior exposure
  - Control group N=98
    - 49 had Zika antibodies
    - 11 had dengue antibodies
  - Hx Dengue not enhance severity of G-B Sx
  - 2 of 10,000 Zika infected developed G-B Sx
  - G-B was more severe but recovery was quicker—4 d vs 2 wk
  - GB is 1-2 per 100,000, M>F, > 50yo, *Camplobacter jejuni*

## Zika confirmed in several Brazil infants w/ microcephaly

Medscape.2016.Zika in newborns.Medscape Feb10., MMWR Morb Wkly Rep.2016;65:63-67.

- disrupted brain growth
- intracranial calcification
- ventriculomegaly,
- neuronal migration disorders (lissencephaly, pachygyria)
- abnormal eye findings
- Congenital contracture
- Clubfoot
- ~75% mothers had Sx consistent w/ zika



- Zika virus testing—do both
  - Reverse transcriptase-polymerase chain reaction on infant serum
  - Zika specific IgM and neutralizing antibodies
- Physical Examination
  - Length, wt, gestational age, head circumference
  - Cranial US
  - Ophthalmologic, hearing at 6 mo
  - Milestones through 12 mo

- Breastfeeding
  - Zika found in breast milk
  - Transmission through breast milk not documented
  - Benefits of breast feeding outweigh theoretical risk

## Other New Viruses in N Am J Neurovirol.2016.Feb 22.Epub.

- Jamestown Canyon
  - Calif, USA---in 10 states, Canada--- 31 cases 200-2013
  - Mosquito---5 species
  - Adults < children
  - Fever, meningitis,

- Powassan
  - USA—GreatLakes, NE; Canada, Russia
  - Tick
  - Tracked 2004-2013
  - 10% fatal if viral encephalitis

- Chikungunya
  - 1952 Tanganyika, Africa
  - USA, Alaska; NOT Canada
  - Mosquito---2 species
  - 2-4 d, fever, arthralgia
  - 1:1000 deaths, mostly elderly
  - > B2
- Expect more in the future---world travel, global warming

# Summary

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# Questions and Discussion

- Thank you