AUTISM - ETIOPATHOGENESIS AND THE ROLE OF INTEGRATIVE APPROACH TO TREATMENT

Presenter - Dr. Shalu Abraham
Chair person – Dr. Rajendra KM
OVERVIEW

- What is autism –
  - a brief glimpse of the concept over the years
  - Risk factors – genetic, epigenetic and environmental
  - Neurobiology of autism

- The role of integrative medicine in diagnosed cases of autism – what is the current evidence

- The role of integrative medicine in perinatal care as prevention of autism – current evidence
The term autism -Eugen Bleuler in 1908.

The Greek word 'autós' meant self and the word “autism” was used to mean morbid self-admiration and withdrawal within self.

In 1940s….the idea of autism changed

The pioneers in research into autism were Hans Asperger and Leo Kanner. They were working separately in the 1940’s.
• 1949-1950
  • Leo Kanner in another study - cause of autism - "refrigerator mother."
  • Bruno Bettelheim claimed that Autism was an emotional disorder - due to psychological harm by parents.

• Towards end of 1960s and in 1970s.....

• Neurobiological basis of autism was suggested

• Bernard Rimland- is a biological condition. He founded the Autism Society of America for parents
Autism over the years

**DSM Criteria for Autism**

- Schizophrenic reaction - Childhood Type
  - Psychotic reaction
  - DSM-I (1952)

- Schizophrenia - Childhood Type
  - Autistic, Atypical, &
  - DSM-II (1968)

- Infantile Autism
  - Infantine Autism
  - DSM-III (1980)

- Pervasive Developmental Disorders
  - Autistic
  - DSM-III-R (1987)

- Pervasive Developmental Disorders
  - Autistic, Asperger's Disorder, PDD-NOS

- Autism Spectrum Disorder
  - Autism Spectrum
  - DSM-5 (2013)
Autism spectrum disorders (ASDs) are a heterogeneous group of biologically based, neurodevelopmental disorders characterized by impairments in two areas.
ETIOPATHOGENESIS OF AUTISM
THEORIES OF AUTISM

• THEORY OF MIND DEFICITS
• Empathising-systemising (E-S) theory
• Weak central coherence theory
• The Extreme Male Brain

• Others=
• The Social Motivation Hypothesis
• The Intense World Hypothesis
What causes AUTISM??

• The mechanisms that lead to autism are at best poorly understood, however they do centre around the disruption of normal cerebral development and its subsequent implications on the functional brain unit

• Although the exact link to the core symptoms remains unascertained.

• Possible factors implicated
  • GENETIC
  • ENVIORNMENTAL FACTORS
  • EPIGENETICS
GENETIC FACTORS - complex genetic underpinnings

**SINGLE GENE DISORDERS**
- Copy number variants and SNVS

**METABOLIC DISORDERS**
- Candidate genes

**Structural chromosomal abnormalities**
- Unknown causes
Fig. 1 Classification of the genetic factors associated with ASD. This figure illustrates the genes responsible for the development of ASD associated phenotype. Na,1.1—sodium channel type 1, Ca,1.2—voltage dependent L-type Ca\(^{2+}\) channel, Kir4.1, and BKCa—potassium channels.
PERINATAL RISK FACTORS

- low birth weight, abnormal gestation length (pre-term delivery) and birth asphyxia (hypoxic-ischaemic insult) (Kolevzon, 2007)
Risk factors- EPIGENETIC

CONGENITAL EPIGENETIC DISORDERS-

• RETTS SYNDROME - caused by mutations in the gene that encode methyl-CpG-binding protein 2 (MeCP2), which is associated with chromatin remodeling. Deficiency of DNA-binding protein or DNA methylation causes Rett syndrome

• PRADER WILLI SYNDROME - Congenital aberrant DNA methylation due to genomic imprinting error causes Prader-Willi syndrome;

• Increased DNA methylation at the promoter regions subsequent reduced expression were observed within the genes of oxytocin receptor (OCTR), Engrailed-2 (EN2) and Reelin (RELN) in the postmortem brain tissues from ASD patients

ACQUIRED EPIGENETIC DISORDERS

• Various environmental factors such as endocrine disrupting chemicals (EDCs), hyponutrition, and mental stress are known to alter epigenetic status
Brain overgrowth –

• Studies have showed **brain overgrowth in first 2 years of life**. Rate of change of total brain volume during second year of life linked to severity of ASD-related social deficits. (Hazlett HC et al 2017) (attributed to PTEN gene).

• A more recent study demonstrated both **accelerated rates of total cortical surface area expansion**, and regionalized expansion in areas in the occipital, temporal, and frontal lobes in infants who later went on to develop ASD.

• **Greater cortical thickness across multiple brain regions** in childhood followed by **crossing of trajectories** in middle childhood and finally reduced regional cortical thickness in early adulthood in individuals with ASD. (Zielinski et al 2014)
• Subcortical structure: Increased amygdala size correlated with the severity of social and communication deficits (Schumann et al 2009). An overall enlargement of subcortical regions in 4-month-old to 6-month-old infants at high familial risk with greater volumes associated with increased restricted and repetitive behaviors at 36 months. (Pote et al 2019)

• Cerebellar abnormalities – observed but inconsistent results

• Corpus callosum - the size of the corpus callosum in individuals who develop ASD is increased compared with controls in the first year of life, normalizes by age 2, and becomes smaller sometime in the third year of life. (Girault et al 2019)

• Extra-axial fluid - increased volumes of extra-axial fluid, in the first year of life in infants go on to develop ASD. Maybe a robust brain biomarker of ASD in early life that deserves further mechanistic study.

• Studies using DTI have demonstrated aberrant white matter abnormalities in the first year of life which accentuate with time
**Brain**
- cortical surface area
- total brain volume
- fractional anisotropy
- extra-axial CSF volume

**Behavior**
- autism prodrome
- emergence of autistic symptoms
  - motor delay
  - atypical visual orienting
  - aberrant response to name / attention to social stimuli
  - repetitive behaviors
  - ASD social deficits

Typical age range for the consolidation of diagnostic criteria for ASD
# BRAIN REGIONS OF POTENTIAL IMPORTANCE IN AUTISM

<table>
<thead>
<tr>
<th>BRAIN AREA</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>Emotional arousal, emotional perception, emotional learning</td>
</tr>
<tr>
<td>Extended amygdala, ventral striatum, nucleus accumbens</td>
<td>Social reward circuity</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>Face recognition</td>
</tr>
<tr>
<td>Posterior superior temporal sulcus</td>
<td>Interpreting non verbal communications, action, observation, theory of mind</td>
</tr>
<tr>
<td>Orbital prefrontal cortex</td>
<td>Emotional learning</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>Social cognition</td>
</tr>
</tbody>
</table>

Comprehensive text book of psychiatry, 10th edition
• **NEUROCHEMISTRY**

- Increase peripheral levels of **serotonin**. The significance is unclear

- **Hyperdopaminergic system** of brain- might explain the overactivity and stereotyped movements seen in autism

- Endogenous opioids – enkephalins and endorphins might lead to social withdrawal and unusual sensitivities to environment
Gut microbiome in ASD

- Gut microbiome is increasing being studied in ASD.
- The commonly reported ASD-associated gut bacteria are Clostridium, Bacteroides, and Desulfovibrio
INTEGRATED APPROACH TO TREATMENT OF AUTISM
Complementary and alternative approaches in ASD

- **Melatonin** - Sleep difficulties affect 50–80% of children with ASD. Supplemental melatonin has improved sleep and behaviour and lowered parent-reported parental stress.

- **Omega-3 Fatty Acid Supplementation** - showing less social withdrawal, less anger, less irritability, more flexibility with spontaneity and none of the side effects.

- **Probiotics** - ‘live microorganism which provide health benefits on host when administered in adequate amounts’

- **Secretin**

- **Vitamins B6, Folate, and B12** = Above average levels of homocysteine have been reported in individuals with ASD, suggesting potential benefits of vitamins involved in homocysteine metabolism.

- **Vitamin C and D**
Complementary and alternative approaches in ASD (contd)

- **Chelation** – purpose to remove heavy metals, but not supported
- **Gluten-Free and Casein-Free Diet** - Asd often have GI disturbances and food insensitivities
- **Ketogenic Diet**
- **Acupuncture**
- **Music Therapy**
- **Hyperbaric Oxygen Therapy**
- **Lifestyle and mind body interventions**
## Yoga for autism

<table>
<thead>
<tr>
<th></th>
<th>Sample size</th>
<th>Research design</th>
<th>Intervention</th>
<th>MAIN outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radhakrishna</td>
<td>N = 6 (5 M, 1 F) (8-14 years) IQ 70 and above</td>
<td>Uncontrolled open trial</td>
<td>Modified Integrated Approach to Yoga Therapy (IAYT) program. Five sessions per week for 10 months.</td>
<td>Improvements in Communication Imitative behaviors Motor control</td>
</tr>
<tr>
<td>(2010)</td>
<td></td>
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<tr>
<td>Radhakrishna</td>
<td>N = 6 (5 M, 1 F) (8-14 years) IQ 70 and above</td>
<td>Uncontrolled open trial</td>
<td>ABA plus modified IAYT program; 15 hr of ABA plus 5 hr of IAYT per week for two 10-month academic years. U</td>
<td>-Increased sitting tolerance -Adult proximity -Subsequent socialization</td>
</tr>
<tr>
<td>(2010)</td>
<td></td>
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</tr>
<tr>
<td>Rosenblatt et al.</td>
<td>N = 24 22 males 2 females ages 3–16 (no IQ cut off)</td>
<td>Uncontrolled open trial</td>
<td>8-week multimodal yoga, dance, and music therapy 45 min session</td>
<td>Improvements on parent-reported BASC-2 • Behavioral Symptom Index (BSI) clinical scale • Atypicality subscale of the BS</td>
</tr>
<tr>
<td>(2011)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Koenig et al.</td>
<td>N = 46 37 males 9 females ages 5–12</td>
<td>Nonrandomized trial with an “education-as-usual” comparison group</td>
<td>Get Ready to Learn (GRTL) program; 16 weeks; daily sessions</td>
<td>Reductions in • Irritability • Lethargy • Hyperactivity • Social withdrawal (scale)</td>
</tr>
<tr>
<td>(2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sootodeh et al.</td>
<td>29 children aged 7 to 15, HFA</td>
<td>Non randomized trial with a control group</td>
<td>an 8-week (24-session) Yoga Training Program (YTP).</td>
<td>significant differences between the two groups with regards to all ATEC sub-scores except ATEC I (speech/language/communication)</td>
</tr>
<tr>
<td>2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Sample size &amp; Diagnosis</td>
<td>Research design</td>
<td>Intervention</td>
<td>MAIN outcomes</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Navarro (2015)</td>
<td>N= 12, 4–7 years, ASDa (DSM-IVTRb, (ADI-Rc, ADOS)</td>
<td>Double blinded RCT Duration: 4 weeks</td>
<td>GFCF</td>
<td>Neither the L/M ratio nor behavioral scores were different between groups exposed to gluten/dairy or placebo.</td>
</tr>
<tr>
<td>Pusponegoro (2015)</td>
<td>N=74, age=4-7 years PDD behaviour inventory, GI SSI</td>
<td>Double blinded RCT Duration: 7 days</td>
<td>GFCF</td>
<td>Administering gluten-casein to children with ASD for one week did not increase maladaptive behaviour, gastrointestinal symptom severity or urinary I-FABP excretion.</td>
</tr>
<tr>
<td>Johnson (2011) (USA)</td>
<td>n = 22 (M 18; F 4) Age: 3–5 years (DSM-IVn and ADOSd)</td>
<td>Randomized, parallel groups Duration: 3 months</td>
<td>GFCF</td>
<td>No significant clinical difference between the two groups (improvement in CBC aggression and CBC ADHD in GFCF group). No improvement in GI disturbances</td>
</tr>
<tr>
<td>Whiteley (2010)</td>
<td>n = 72 (gender not reported) Age: 4–11 years (ADOSd, ADIRc)</td>
<td>Double blind RCT with crossover Duration: 24 months</td>
<td>GFCF</td>
<td>Significant improvement in the diet group at 12 and 24 months in ADOS communication (P = 0.002) and repetitive domains, GARS social domains (P = 0.0001). Improvement in inattention and hyperactivity symptoms (0.0007)</td>
</tr>
<tr>
<td>Elder (2006) (USA)</td>
<td>n = 15 (M 12; F 3) Age: 2–16 years (DSMIVn, ADI-Rc)</td>
<td>double blind RCT crossover Duration: 12 weeks</td>
<td>GFCF</td>
<td>No significant differences between the two groups</td>
</tr>
<tr>
<td>Knivsberg (2002) (Norway)</td>
<td>n = 20 (gender not reported) Age: 59–127 months</td>
<td>Single blind RCT Duration: 12 months</td>
<td>GFCF</td>
<td>Improvement in domains of autism and motor control</td>
</tr>
</tbody>
</table>
## Dietary supplements

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Number of studies</th>
<th>Beneficial effect</th>
<th>Disadvantages/limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylcysteine</td>
<td>3</td>
<td>3/4 (75%)</td>
<td>Discordance in dosage of supplement used in each study, concurrent use of risperidone</td>
</tr>
<tr>
<td>Eicosapentaenoic &amp; dososahexaenoic</td>
<td>3</td>
<td>0/3 (0%)</td>
<td>Heterogeneity in treatment duration/sample size</td>
</tr>
<tr>
<td>Pyridoxine + Mg</td>
<td>4</td>
<td>1/3 (33%)</td>
<td>High heterogeneity in dosage of supplement/sample size/treatment duration</td>
</tr>
</tbody>
</table>
Ayurveda in autism

- Very limited publications

- **AYURVEDIC INTERVENTIONS IN AUTISM SPECTRUM DISORDERS –A CASE SERIES –Lekshmi MK( International journal of Ayurveda and Pharma Research 2016)**

- 10 cases diagnosed with Childhood Autism Rating Scale (CARS) and the treatment outcome was measured by Autism Treatment Evaluation Checklist (ATEC).

- The Ayurvedic treatment protocols for the cases selected were according to Dosha predominance of the condition at that time. All of the children considered for the case series were receiving speech as well as psycho therapies and appropriate dietary advice and assessment was done after three months. **Treatment consisted on 2 weeks of OP treatment (Deepana and Sadhysnehapana) followed by 3 weeks of IP care (oil massage and fomentation, medicated enema, slow pouring of oil on head), followed by at home treatment (3 weeks of herbal paste application on head) and later one month of oral medication**

- The change in CARS score was highly significant at 0.05% level (P<0.0005). Also the change in ATEC and sensory parameters was significant at 1% level (P<0.01). The treatment has significant effect on sociability (t=2.662,P<0.05) and physical features (t=2.436,p<0.05)
### Integrated approach of treatment to autism

**EVIDENCE**

<table>
<thead>
<tr>
<th>Safe</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>
| Yes  | Recommend:  
Healthy Lifestyle  
ABA, PIT  
Melatonin for sleep  
Music Therapy  
Neurofeedback  |
|      | **Tolerate:**  
Multiple essential nutrients  
Vitamins B6, B12, C, D and folate; omega-3 fatty acids; probiotics  
Sensory and auditory integration  
Animal-Assisted Therapy  
Hydrotherapy  
Yoga  
Massage  
Chiropractic  
Acupuncture  
TMS  |
|      | **Monitor:**  
Medications (risperidone, aripiprazole) for problematic irritability  
GFCF diet  
Other restrictive diets  |
| No or not established in 2 or more RCTs | **Avoid:**  
Hyperbaric oxygen  
Secretin  
Chelation |

Klein et al 2016
Integrated approach in perinatal period for prevention of autism
Critical periods of susceptibility

• Timing is critical for neurodevelopment, and hence for studying environmental impacts.

• Multiple critical periods of increased susceptibility for ASD likely exist and may extend from pre-conception through the first few years of life.
<table>
<thead>
<tr>
<th>Trimester</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Weeks</strong></td>
<td>1-20</td>
<td>21-28</td>
<td>29-38</td>
</tr>
</tbody>
</table>

**Brain pathology**

<table>
<thead>
<tr>
<th>Event</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenesis</td>
<td>Weeks 1-20</td>
</tr>
<tr>
<td>Neuronal migration</td>
<td>Weeks 1-16</td>
</tr>
<tr>
<td>Neuronal maturation</td>
<td>Weeks 1-24</td>
</tr>
</tbody>
</table>

**Exposure**

<table>
<thead>
<tr>
<th>Event</th>
<th>1st, 2nd, and 3rd trimesters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeway proximity</td>
<td>3rd trimester</td>
</tr>
<tr>
<td>Traffic-related Air Pollution</td>
<td></td>
</tr>
<tr>
<td>Pesticides</td>
<td>Days 26-81</td>
</tr>
<tr>
<td>Prenatal vitamins</td>
<td>1st month and 3 months before</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1st month</td>
</tr>
<tr>
<td>Rubella infection</td>
<td>Weeks 1-8</td>
</tr>
<tr>
<td>Fever</td>
<td>1st and 2nd trimesters</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Days 20-24</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Day 20-24</td>
</tr>
<tr>
<td>SSRI</td>
<td>1st trimester</td>
</tr>
<tr>
<td>Prenatal stressors</td>
<td>Weeks 25-28</td>
</tr>
</tbody>
</table>
**PERINATAL RISK FACTORS**

- **Pre-gestational and gestational diabetes mellitus (GDM)** in the mother is associated with ASD in the offspring (Xiang et al. 2015), (Ornoy et al. 2016). The risk increases when associated with **maternal obesity** (Connoly et al. 2016).

- ASD was associated with both **inter-pregnancy interval (IPI) of less than 18 months** (aOR 1.5 [1.1–2.2]) and **greater than 60 months** (1.5 [0.99–2.4]). (data from SEED study)

- A Swedish study found **parental autoimmune disorders**, particularly maternal type I diabetes, idiopathic thrombocytopenic purpura, myasthenia gravis, and rheumatic fever, were weakly but significantly associated with offspring ASD (A Keil et al. 2010). **Anti-fetal brain autoantibody (Ab+)** is shown to be present in **25% of 227 mothers of children with ASD** in the Childhood Autism Risk from Genetics and the Environment (CHARGE) study (Krakowiak et al. 2016).

- A meta-analysis of 27 studies found that **advanced parental age** was associated with an increased risk of autism in the offspring, with adjusted ORs 1.41 (95% CI 1.29–1.55) and 1.55 (95% CI 1.39–1.73) for mother and father, respectively.
The CHARGE study collected exposure information and found that ASD was associated with *maternal fever during pregnancy*. Furthermore, fever-associated ASD risk was reduced among mothers who took antipyretic medications. (the association may be related to induction of inflammatory mediators rather than the viral illness itself) (Zerbo et al 2013)

**ENVIRONMENTAL RISK FACTORS**

- **Air pollution** - a systematic review and meta-analysis of over 1000 references concluded that evidence of the association of air pollutants and risk of ASD was limited, the *strongest evidence was for the association between prenatal exposure to particulate matter and ASD.* (J Lam et al, 2016)

- **Insecticides** - From the CHARGE case-control study, proximity of the mother during pregnancy to *organophosphate pesticide* application was associated with a 60% increase in odds of ASD. Particular risk was conferred during the 2nd trimester (OR = 3.3; 95% CI: 1.5, 7.4) and 3rd trimester (OR = 2.0; 95% CI: 1.1, 3.6).

- **Heavy metals** - Pregnant mothers living close to industrial facilities releasing lead, mercury, and arsenic, have increased offspring ASD risk (Miodovnik et al 2011). A comprehensive review of 91 studies focusing on the association of *mercury and ASD* found that 74% suggest mercury as a risk factor for ASD (J.K kern et al 2016)
Substance and drugs

- **Valproic acid** - review of prescription data, psychiatric registers, and birth records from 655,615 Danish children, found increased ASD risk in the 508 children who were exposed to valproic acid in utero, with a hazard ratio of 2.9 (95% CI: 1.4–6.0) (Christensen et al 2013)

- **Thalidomide** – historically associated with asad

- **SSRI** – results have contradicting results

- **Acetaminophen** - A meta-analysis of seven studies found increased risk for ASD (Risk Ratio = 1.23, 95% CI 1.13,1.32, I2 + 17% (Masarwa et al 2018)

- **Cigarette Smoking** - A number of investigations have assessed maternal smoking in association with ASD, each with limitations, and overall producing inconsistent findings (Lyall et al 2014)

- **Alcohol Use** - The relationship of maternal alcoholism to ASD are conflicting. In the largest study of prenatal alcohol exposure and ASD risk, in a population-based cohort of 80,552 Danish children and their mothers, average self-reported alcohol consumption was not associated with either ASD or infantile autism. OTHER SUBSTANCES- lack of research data
Labor and delivery risk factors

- **Cesarean section (CS)** is significantly associated with an increased odds for ASD (OR: 1.26, 95% CI: 1.22–1.30) after adjusting for gestational age, site, maternal age and birth year (BHK yip et al 2017).

- **Augmentation of labor with oxytocin** is found to be modestly associated with an increased risk for autism in males (HR 1.13; 95% CI, 1.00–1.26; P = 0.04) in a sample of 557,040 children in Denmark (not confirmatory)(Weisman et al 2015).
### ASD perinatal risk factors and possible interventions

<table>
<thead>
<tr>
<th>RISK FACTORS</th>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal and gestational diabetes</td>
<td>Glucose control?oxidative stress, inflammatory process</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Diet, exercise</td>
</tr>
<tr>
<td>Birth spacing</td>
<td>&gt;18 &lt;60 months</td>
</tr>
<tr>
<td>Autoimmune and inflammatory Disorder</td>
<td>Treat the autoimmune disorder and inflammation</td>
</tr>
<tr>
<td>Advanced Paternal and maternal age</td>
<td>Programs to improve immunity and health</td>
</tr>
<tr>
<td>Maternal infection and fever</td>
<td>Reduce fever?antibiotic/antipyretics</td>
</tr>
<tr>
<td>Air pollution</td>
<td>Limit exposure, improve immunity</td>
</tr>
<tr>
<td>Environmental chemicals</td>
<td>Limit exposure, improve immunity</td>
</tr>
<tr>
<td>Medications</td>
<td>Risk–benefit for use</td>
</tr>
<tr>
<td>Labor and delivery complication</td>
<td>Prenatal, labor, delivery skilled care</td>
</tr>
<tr>
<td>Postpartum depression and stress</td>
<td>Vigilance and appropriate intervention</td>
</tr>
</tbody>
</table>
Interventions that may improve neurodevelopmental outcome

- **FOLIC ACID** — 40% reduction in risk for ASD* (Schmidt RJ et al 2011), significant trend of decreasing ASD risk as mean daily folic acid intake increased (Schmidt RJ 2012), $\geq 600$ ug of folic acid was associated with protection only when either the mother or the child carried a common variant in the methylenetetrahydrofolate reductase gene, $MTHFR$ 677 C>T

- **FISH AND FISH OIL SUPPLEMENTS** - Also be relevant to neurodevelopment and ASD, both as a source of fatty acids and vitamin D (which may confer protective effects) and as a potential source of mercury (which is deleterious to fetal brain development).

- **FATTY ACIDS** - higher intake of polyunsaturated fatty acids (PUFA) before and during pregnancy had reduced risk of ASD (Lyall K et al 2013)

- **VITAMIN D** - Low maternal (and thus fetal) vitamin D levels have been hypothesized as risk factors for ASD, based on reports of increased rates of ASD among children of dark-skinned immigrant mothers who moved to high latitudes (Dealberto MJ 2011) and among children born or conceived in certain season (Zerbo O 2011)
• **MULTIVITAMIN AND NUTRITIONAL SUPPLEMENTATION** - A prospective cohort study of more than 200,000 mother-child pairs found lowered prevalence of ASD with intellectual disability in children born to mothers who reported multivitamin (MV) supplementation during pregnancy, compared to mothers who reported no MV, iron, or folic acid supplementation (OR: 0.69, 95% CI: 0.57–0.84) (Devilbis et al 2017)

• **IODINE AND THYROID INTERVENTIONS** - The presence of the maternal anti-thyroid peroxidase antibody during gestation is associated with verbal, perceptive, cognitive and motor disturbances, as well as almost 80% increase in the odds of having an offspring with autism (OR = 1.78, 95% CI = 1.16–2.75, p = 0.009) (Brown et al 2015)

• **IRON** - A CHARGE study examined maternal iron intake and risk of ASD in the children. Findings showed that the highest iron intake was associated with reduced ASD risk, especially during breastfeeding(Schmidt et al 2014)
• **BREASTFEEDING**- Breastfeeding, through the transference of oxytocin in breast milk, is shown to contribute to social recognition, social bonding, and neurodevelopment in the infant (Krol et al 2015). Sub-optimal breastfeeding is associated with risk of ASD, as well as other behavioral and cognitive deficits.(Y.M. Al-Farsi et al 2012)

• **POSTPARTUM DEPRESSION AND STRESS**- The psychotropic drugs are generally considered safe to use postpartum studies on the relationship between maternal use of antidepressants during pregnancy and development of ASD in children are inconclusive
<table>
<thead>
<tr>
<th>Agent</th>
<th>Evidence*</th>
</tr>
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<tbody>
<tr>
<td>Folic and Folinic Acid</td>
<td>Grade B; Moderate Certainty</td>
</tr>
<tr>
<td>Omega-3 PUFA</td>
<td>Grade B; Moderate Certainty</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Grade B; Moderate Certainty</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>Grade B; Moderate Certainty</td>
</tr>
<tr>
<td>Iron</td>
<td>Grade C; Moderate Certainty</td>
</tr>
<tr>
<td>Choline</td>
<td>Grade C; Low</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Grade B; Moderate</td>
</tr>
</tbody>
</table>

* U.S. Preventive Services Task Force Quality Rating Criteria

Summary

- Autism is a neurodevelopmental disorder
- Complex interplay of genetics, environmental and epigenetics
- No definite cure for ASD
- Maximum evidence for behavioural interventions
- CAMH is increasingly being used in ASD
- Lack of systematic study is major limitation for the CAMH practices.
- Primary prevention should be the focus whenever possible.
Thankyou
A number of peer-reviewed papers have been produced as a result of this study. They have concluded that:

- There is an association between living near a freeway and risk of autism.

- No association was found between blood levels of mercury and autism among a group of children studied at two-to-five years of age.

- There is an association between exposure to traffic-related air pollution and autism risk.

- There may be a causative link between both exposure to air pollution, a variant in the MET receptor tyrosine kinase gene and risk of autism.

- Maternal use of folic acid supplements may be associated with a decreased risk of autism. However, the researchers cautioned that further research is warranted to confirm or refute this finding.

- Maternal fever during pregnancy is associated with an increased risk of autism in her child.

- Gastrointestinal problems are significantly more common in children with autism than children without autism.