An Historical Perspective on Caring for Mothers with Substance Use Disorders and Babies with Neonatal Abstinence Syndrome

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National Perinatal Association
Loma Linda Children’s Hospital, California
Disclosure

To the best of my knowledge, I have no relevant disclosures. Information to be presented derives from relevant research and accepted protocols based on research accomplished by me, colleagues and other researchers.

Loretta P. Finnegan, M.D., LLD, (Hon.), ScD (Hon.)
Executive Officer, College on Problems of Drug Dependence, Inc., President, Finnegan Consulting, LLC
Professor of Pediatrics, Psychiatry and Human Behavior, Thomas Jefferson University (Retired)
Founder and Former Director of Family Center, Comprehensive Services for Pregnant Drug Dependent Women, Philadelphia, Pennsylvania
Former Medical Advisor to the Director, Office of Research on Women's Health, National Institutes of Health, United States Department of Health and Human Services (Retired)
Issues to Consider

• Historical references
• Background regarding opioids and the epidemic
• Progress in defining NAS
• Current assessment & treatment methods
• Characteristics of methadone influencing NAS
• Concluding comments
“The one who does not remember history is bound to live through it again.”

Georges Santayana, Spain (1863-1952)
Factors Affecting ONSET of Neonatal Abstinence

Murdina Desmond, 1965, Jackson Memorial Hospital, Houston, Texas

- Type of drug utilized by the mother (*heroin vs methadone*)
- Maternal poly-drug use (*variable onsets*)
- Timing of the dose of opioid before delivery (*sooner or later*)
- Character of the labor (*short vs. long*)
- Type and amount of anesthesia and analgesic given during labor and delivery (*epidural-less interference*)
- *Maturity of the infant (term vs. preterm)***
- Nutritional status of the infant (*term vs. IUGR*)
- Presence of intrinsic disease (*the sick infant*)
Historical Background I

• Theory: 1800’s--“Infants are unaffected by opioids-- morphine use among women was associated with sterility and a loss of sexual desire.”

• 1850--First mention of drugs as a “problem” for babies.

• Late 19th century---2/3 of drug dependent individuals in America were women----stereotype was white, Southern genteel, middle-upper class; drug use and dependence supported by physicians and pharmacists. Women given opiates for general illnesses—”female problems”, neurasthenia— (As a psychopathological term, neurasthenia was used by Beard in 1869 to denote a condition with symptoms of fatigue, anxiety, headache, heart palpitations, high blood pressure, neuralgia, and depressed mood.)
Women, Drugs and Addiction
Late 19th Century
Historical Background II

• 1875--first reported case of NAS in a newborn who manifested signs of opioid withdrawal at birth; diagnosis: \textit{congenital morphinism. No treatment; infant died.}

• 1892--12 affected babies reported, \textit{9 died; no specific treatment was offered.}

• 1885-Jayne’s Carminative -contained large amount of alcohol and some opium—a cure for all ills.
Neonatal Abstinence Syndrome 1901

• Due to a lack of knowledge of the cause of the signs of NAS, it was frequently fatal to newborns.

• 1901-- recognized that clinical signs were the result of the infant withdrawing from the cessation of the passive transfer of maternal morphine and that providing the infant with medication would ease his/her signs.

• Infants were given opium in small quantities to treat their signs with reports of success;

• 1901-- Breastfeeding was encouraged as it helped “calm the babies” and in some occasions ease their signs without pharmacological intervention; improvement in decreasing NAS signs and hospital stay and improving maternal-infant attachment most probably due to the soothing effect of breastfeeding;

• 1903-- report described survival of a neonate after morphine treatment;
Historical Background III

• 1947—Successful treatment of seizures reported in an infant with congenital morphinism; methadone approved for use in the US;

• 1953-55—Report of 18 infants with NAS, 25% mortality—
  prematurity, respiratory failure, Rx-methadone,
  Phenobarbital, paregoric

• 1956—Series of 32 babies reported-50% premature;
  34-93% mortality

• Congenital Morphinism remained a medical curiosity and was subsequently renamed Neonatal Abstinence Syndrome (NAS)
Historical Background IV

- **1965** -- Goodfriend et al report neonatal withdrawal signs
- **1965** -- Desmond and Wilson– “Neonatal Abstinence Syndrome: Recognition and Diagnosis”
- **1971** -- Zelson et al reported frequency of signs of neonatal withdrawal and days of treatment needed--4% mortality
- **1971** -- Methadone withdrawal reported in 5 newborns
- **1975** -- Lipsitz publishes “The Neonatal Drug Withdrawal Scoring System” (June); Finnegan publishes the “Neonatal Abstinence Syndrome Score” (January);
Exposed to heroin in utero "What can I do for you, baby?” IDEA! Start to help you in utero--Helping your Mommy will help you. Circa 1969


Figure 1. Family Center schema for the treatment of drug dependency in the perinatal period and aftercare

Outreach Services
- Community Liaison
  - Indigenous Workers
  - Mobile Van
  - Distribution of Prevention and Educational Information
  - Work with Community Organizations, Churches, Recreational Centers, etc.

Case Management
- Linking other Social Services Systems
- Facilitation of Services
- Advocacy for Services

Immediate Access to Treatment
- Private Transportation
- Coordinates Intake
- Medical
- Drug Treatment
- Psychiatric Evaluation

Individual and Interpersonal (Group, Family and Other)

Outpatient Services

Residential Treatment
- Vocational/Educational

Socio/Cultural/Demographic
- Life Skill Management
  - Definition and Assessment of Problems Associated with Addiction
  - Attitudes, Beliefs, Knowledge and Expectation Modification
  - Problem Solving
  - Coping Mechanisms
  - Relapse Prevention
  - Social Skill Competence
  - Educational - Prenatal, Parenting Skills, Child/Parent Attachment, AIDS, Child and Adult Development, Physical Development, Nutrition

Survival Management
- Housing
- Clothing
- Food
- Financial and Budgetary
- Vocational, Educational

Social Service Liaison
- Negotiation of Social Service System
- Facilitation of Services with Social Agencies, DHS, DPW, WIC, Judicial System

Early Childhood Development Program

Mother-Infant Development
- Eliminating Intergenerational Substance Abuse
- Sociological Considerations
  - Gender
  - Race
  - Social Class
  - Economics
  - Culture

Maternal-Infant Relationship
- Assess Cognitively-Impaired
  - Intervention Strategies to Meet Individual Mother-Infant Needs
  - Facilitate Caregiver Needs in Relation to Environmental Realities

Intervention Services
- Intervene in Unresponsive and Dysfunctional Maternal Behaviors
- Encourage Optimal Social, Emotional and Cognitive Development of Children Born to Drug Dependent Mothers
- Promote Parenting Skills
- Provide Child Care

Biological/Physiological
- Genetic
  - Medical

Psychological/Behavioral/Cognitive
- Prenatal Services
  - Comprehensive Prenatal Care
  - HIV Counseling and Testing
  - Nutritional Counseling
  - Antenatal Testing

- Perinatal Services
  - Obstetrical Services
  - Pediatric Services
  - Medical Developmental, Emotional Neonate Assessment
  - Family Planning

- Pharmacological
  - Medication Maintenance
  - Psychotropic Medication

- Other Medical Education and Referral
  - Medical Problems Associated with Addiction
  - Medical Problems Associated with Poverty

From Finnegan et al., 1991
Components of Comprehensive Drug Abuse Treatment

Principles of Drug Abuse Treatment (A Research Based Guide) NIDA, NIH publication # 09-4180, April 2009
Historical Background V

- **1997**--First reported case of buprenorphine withdrawal in newborns.

- **1995 to 2009**--Opioid prescriptions for pain management in pregnant women doubled;

- **2001**--Buprenorphine withdrawal reported in 13 newborns.

- **2002**--First reported case of oxycontin withdrawal in newborns.

- **2012**--Opioid prescriptions shifted to the treatment of chronic pain resulting in a steep increase in their abuse;

- **2015**--An estimated 2 million people living in the United States with a SUD related to prescribed opioids; **Shift in prescribing:** estimated 591,000 people with heroin use disorder and approximately 13,000 deaths related to overdose;
Continued concern about perinatal dependence
(5 fold increase in NAS between 2000-2015)
NAS and Associated Health Expenditures 2000-2009

Patrick, S et al. JAMA, May 9, 2012—Vol 307, No. 18

- **Cost of care for NAS 2009**
  - NAS = $53,400
  - All other births = $9,500

- **Proportion of NAS paid for from Medicaid**
  - 2002 = 69%
  - 2009 = 78%
Historical Background VI

• **2000-2017**—Epidemic of NAS causes growing concern.

• Numbers increased from *one baby in 1875* to 2012 when the incidence of NAS increased to more than 30 per 1000 live births; Increases in the number of infants being treated pharmacologically resulted in an increase in the length of stay and *healthcare expenses.*
More reason for concern...

91 Americans die each day from an opioid-related overdose.”

Centers for Disease Control and Prevention 2017
Exposure to Opioids in Utero
What do we know? What is the recent research?
Where do we go from here?
Addiction is a Brain Disorder

Through decades of scientific study of the brain, behavior, genetics, and physiology, we now know that addiction is a complex disorder affected by neural function, genes, and the environment.

Addiction is a chronic relapsing disease with medical, psychiatric, and sociological ramifications.
Ingredients of Addiction

- Physical dependence
- Psychological Dependence
- Tolerance
- Compulsion to seek and take the drug(s) no matter how detrimental it may be to them or society
Risks to Infants Born to Opioid Dependent Women without Prenatal Care

- Prematurity
- Intrauterine Growth Restriction
- Neonatal sepsis
- Stillbirth
- Perinatal Asphyxia
- Congenital malformations (with concomitant alcohol abuse-- potential for life long disabilities)

- Poor mother–infant attachment
- Deprivation
- Neglect/FTT
- Child abuse/sexual abuse
- Sudden Infant Death Syndrome (SIDS)
Opioids easily pass from mother to fetus…(low molecular weight, lipid solubility). Clamping the umbilical cord interrupts the drug supply, creating a 60-80% chance for Neonatal Abstinence Syndrome
What is Neonatal Abstinence Syndrome?

A generalized disorder of 4 systems with a clinical picture of:

- **Central Nervous System** (irritability, high pitched cry, tremors, hypertonia, hyperreflexia, sleep disturbances)
- **Gastrointestinal System** (regurgitation, loose stools, dysrhythmic sucking and swallowing, poor intake with weight loss)
- **Respiratory System** (excessive secretions, nasal stuffiness, tachypnea)
- **Autonomic Nervous System** (sweating, sneezing, yawning, hyperthermia)

**(Hyperactivity, vomiting, diarrhea, increased insensible water loss usually leads to excessive weight loss, suboptimal weight gain)**
Just because babies have withdrawal signs, does this mean that they are born addicted?
Are babies addicted?

- To call babies "addicted" is stigmatizing and incorrect.
- Babies don't have compulsive drug seeking behavior in spite of adverse consequences.
- They do have a transient but potentially serious **physiologic disturbance** from abrupt discontinuation of prenatal opioid exposure when the umbilical cord is cut.
What Neonatal Abstinence is NOT!

- “Born Addicted”
- “Hooked Newborns”
- “Littlest Victims”
- “Heroin Babies”
- “Addicted Babies”
- “Oxy Babies”
- “Oxy Tots”
- “Tiny Addict”
- “Methadone or Bup Babies”
Drugs which produce “neonatal abstinence/withdrawal”—NAS or NOWS?

- **Opioids**: *opium, *morphine, meperidine (Demerol), methadone, heroin, oxycodone (Oxycontin), hydrocodone (Vicodin), hydromorphone (Dilaudid), [also extended release (Palladone)], codeine, pentazocine, Fentanyl, propoxyphene (Darvon), *buprenorphine
- Alcohol, barbiturates, caffeine
- Selective serotonin reuptake inhibitors: citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), also venlaxafine (Effexor)
- Others: tricyclic antidepressants: clomipramine (Anafranil), desipramine (Pertrofan, Norpramin)
- Chlordiazepoxide (Librium). Diazepam (Valium), diphenhydramine (Benadryl), ethchlorvynol (Placidyl), glutethimide (Doriden), hydroxyzine (Atarax), meprobamate (Miltown, Equanil)
Although we think of drug use in a singular fashion, *i.e.*, opioids, **multiple drug use** is more common in pregnant women and effects upon the fetus are compounded.
Neonatal Abstinence Syndrome: a potentially serious medical condition

• Effects vital functions in the neonatal period that permit growth and normalcy such as:
  • *Feeding*
  • *Elimination*
  • *Sleep*

• Signs mimic other serious neonatal conditions
Serious neonatal conditions presenting with signs similar to NAS

- Septicemia, encephalitis, meningitis
- Post-anoxic CNS irritation
- Hypoglycemia
- Hypocalcemia
- Cerebral hemorrhage
Can Neonatal Abstinence cause death of a newborn infant?

Unrecognized/untreated NAS can result in death from:
- excess fluid losses
- hyperpyrexia, seizures
- respiratory instability
- aspiration and apnea
- **But NOT in 2018**
Persistent Signs of Neonatal Abstinence
(Duration may be as long as 6 months and more)

- Hyperphagia with increased oral drive
- Sweating
- Hyperacusis
- Irregular sleep patterns
- Loose stools
- Poor tolerance to holding or to abrupt changes of position in space
NAS is a Complex Issue -- but understanding it and using sound principles makes it easy for the baby and the treating medical professionals.
How do we assess withdrawal in the baby?
A Basic Principle in Assessing NAS is to Utilize a Scoring Tool


<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Time</th>
<th>AM</th>
<th>PM</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Central Nervous System Disturbances</strong></td>
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<tr>
<td>Crying: Excessive High Pitched</td>
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<tr>
<td>Crying: Cont. High Pitched</td>
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<tr>
<td>Sleeps &lt; 1 Hr After Feeding</td>
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<td>Sleeps &lt; 2 Hr After Feeding</td>
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<td>Sleeps &lt; 3 Hr After Feeding</td>
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<td>Hyperactive Moro Reflex</td>
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<tr>
<td>Markedly Hyperactive Moro Reflex</td>
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<tr>
<td>Mild Tremors: Disturbed</td>
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<td>Mod Severe Tremors: Disturbed</td>
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<tr>
<td>Mild Tremors: Undisturbed</td>
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<td>Mod Severe Tremors: Undisturbed</td>
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<tr>
<td>Increased Muscle Tone</td>
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<td>Excoriation (Specific Area)</td>
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<tr>
<td>Myoclonic Jerk</td>
<td>5</td>
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<tr>
<td>Generalized Convulsions</td>
<td>5</td>
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<tr>
<td><strong>Metabolic, Vasomotor And Respiratory Disturbance</strong></td>
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<tr>
<td>Sweating</td>
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<tr>
<td>Fever &lt; 101 (37.2-38.3c)</td>
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<tr>
<td>Fever &gt; 101 (38-4c)</td>
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<tr>
<td>Frequent Yawning (&gt; 3)</td>
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<td>Morining</td>
<td>4</td>
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<tr>
<td>Nasal Stiffness</td>
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<td>Sneezing (&gt; 3)</td>
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<tr>
<td>Nasal Flaring</td>
<td>7</td>
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<tr>
<td>Respiratory Rate (&gt; 60/MIn)</td>
<td>8</td>
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<tr>
<td>Respiratory Rate (&gt; 60/MIn With Retractions</td>
<td>9</td>
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<tr>
<td><strong>Gastrointestinal Disturbances</strong></td>
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<tr>
<td>Excessive Sucking</td>
<td>1</td>
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<tr>
<td>Poor Feeding</td>
<td>2</td>
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<tr>
<td>Regurgitation</td>
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<tr>
<td>Projectile Vomiting</td>
<td>4</td>
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<tr>
<td>Loose Stools</td>
<td>5</td>
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<tr>
<td>Watery Stools</td>
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<tr>
<td><strong>Total Score</strong></td>
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</table>
But why a neonatal score, scale or index instead of good clinical evaluations?

• *Scores to assess abstinence are useful for adults but those are not feasible for babies.*

• With the undulating pattern of signs in the neonate vacillating from exacerbations of vigorous movements to sleep from exhaustion, a *24/7 assessment is necessary (not twice daily as with some reports).*

• *Specific guidelines are needed as an aid to clinical management to assess the severity of symptoms and the potential need for pharmacotherapy* (Green and Suffet, 1981).
Characteristics of a good neonatal score, scale or index

• Scores permit administration of care systematically and selectively with avoidance of prolonged need for medication and hospital stay. (if administered correctly)

• A score allows for a “common language”, decreased variability, and improves parent communication and involvement.

• Scores permit the clinician to observe any progression of signs before the baby could be in danger.
Methods of scoring severity of NAS have been used for the investigation of:

- Effectiveness of therapeutic drugs (Kahn et al. 1969)
- As an aid in the study of sucking behavior (Finnegan et al 1975)
- To study the relationship between maternal methadone dosage, neonatal environmental factors, and intensity of abstinence in the baby (Ostrea et al 1976)
- Experience with the aid of a score for NAS can improve clinical acuity (Finnegan et al 1975)
Ingredients of a useful score...

• **Tested in large numbers of babies** undergoing abstinence and those **not** exposed to any maternal opioids. (natural childbirth)

• Accurately assesses opioid–exposed infants for the presence of abstinence signs; **used in many clinical settings**.

• **Validation**—Assessment of infants with NAS needs to be standardized and the chosen assessment tool needs to have strong clinimetrics rather than psychometric properties.

**Clinimetric**—The practice of assessing or describing symptoms, signs, and laboratory findings by means of scales, indices, and other quantitative instruments.

Ingredients of a useful score II

• **Definitions provided** for each item scored with descriptions of appropriate **examination techniques** required to evaluate NAS (manual).

• Signs evaluated are the traditional signs with **no redundancies and no diagnoses** listed.

• **Reliability testing to achieve 90% reliability** with other examiners in using the score.

• After orientation, **score can be done in 4-5 minutes**
Are cut off numbers correct in FNAS Score?

• For the FNAS score, 200 babies, non drug exposed and born by natural childbirth with no analgesics/anesthetics given to the mother were scored. Scores were between 0 and 5.
• An evaluation of the validity of the cut-off points of the FNAS score was made by Zimmermann et al.
  • They applied the FNAS score to infants without a history of opioid exposure and found that scores ≥ 8 should be considered pathological. Infants without opioid exposure commonly have scores < 8 and, if a score of 8 is found in only one evaluation, they subsequently became normal.
• This finding validates the FNAS guideline of requiring 3 continuous abnormal scores to consider pharmacological treatment.
In assessing and treating NAS, do NOT procrastinate in initiating treatment. Prompt escalation of dose, with aggressive decreases in dose as symptoms abate are essential principles. Babies with NAS completely recover. The clinician’s Patience and Wisdom are key!
Treatment of NAS must take into consideration factors that have been shown to enhance the expression of NAS and effect the response of infants to non-pharmacological and pharmacological interventions. These include neonatal (gestational age, neonatal metabolism, genetic predisposition and epigenetics), maternal (smoking, type, length, quality and quantity of the used drug, SSRI use and the enrollment in Medication Assisted Therapy) and external factors (decision to breastfeed and rooming-in possibility).
NAS Pharmacological Therapy: Practice

- NAS therapeutical practices may significantly vary from practice to practice and hospital to hospital.\(^1\)
- Morphine is the dominant therapy for NAS treatment.\(^1,2\)

**Medication Used as First-line NAS Treatment in 14 Hospitals, 2004-2011**

- Other 1.4%
- Methadone 33.6%
- Combination of Methadone and Morphine 1.4%
- Morphine 42.3%
- Phenobarbital 18.9%
- Benzodiazepine 3%

- 34%
- 42%
- 19%

**Medication Use in infants with NAS**

Patrick et al. 2014

Tolia et al. 2015
Pharmacological Treatment of NAS

- **Abstinence from opioids**: *oral morphine* or *methadone* (AAP) according to body weight and score; *clonidine* (limited data); *Buprenorphine*, (Kraft et al in Philadelphia, PA)

- **Abstinence from other substances** (e.g. barbiturates, ethanol, sedative hypnotics), *Phenobarbital* generally administered;

- No definitive answer as to the best drug; RCT in progress;

94 % of UK and 83% of US physicians use morphine or methadone to treat NAS.
# Morphine Dosing Guidelines for NAS

Child Health Network, Toronto 2002

<table>
<thead>
<tr>
<th>Score</th>
<th>Morphine Daily Dose in four divided doses</th>
<th>Morphine Single Dose</th>
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<tbody>
<tr>
<td>8-10</td>
<td>0.32 mg/kg/day</td>
<td>0.08 mg/kg</td>
</tr>
<tr>
<td>11-13</td>
<td>0.48 mg/kg/day</td>
<td>0.12 mg/kg</td>
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<tr>
<td>14-16</td>
<td>0.64 mg/kg/day</td>
<td>0.16 mg/kg</td>
</tr>
<tr>
<td>17+</td>
<td>0.8 mg/kg/day</td>
<td>0.2 mg/kg</td>
</tr>
</tbody>
</table>
Supportive Measures

Finnegan, L. and MacNew, B., Care of the Addicted Infant, American Journal of Nursing, 74: 685, 1974

- Offer a pacifier (Non-Nutritive Sucking)
- Skin to skin contact with mother (Cuddler)
- Do not overdress the baby
- Positioning baby to right side-lying to reduce aspiration if vomiting or regurgitation is a problem
- Aspirate naso-pharynx
- Feed small amounts frequently (q 2hrs) if poor feeding persists-do not over feed
  - Swaddling snugly with hands available for sucking (“Safe Sleep” campaign is supine positioning without swaddling; strategy: side positioning with light swaddling)
Eat, Sleep & Console
Alternative Treatment Approach for Neonatal Abstinence Syndrome
Low stimulation environment, rooming in and frequent feeds.
Eat, Sleep & Console

(comments regarding the initial publication)

Lipshaw, M., PAS Meeting, May, 2017; Grossman, M et al., An Initiative to Improve the Quality of Care of Infants With Neonatal Abstinence Syndrome, Pediatrics 2017;139;

• Few babies needed medication when on ESC; Morphine Rx-FNASS-60%; ESC-12%
• Decrease in LOS from 22.5 to 5.9 days
• No babies readmitted but no formal follow-up; Necessary to follow for at least 6 months—Method used for follow-up very vague;
• 50 babies studied; Assessment very subjective-inter-rater reliability? Used a historical comparison; No assessment of GI symptoms;

• What about potential “brain repair” after opioid exposure which may need the pharmacological treatment.
• Recommendations in 1975 FNASS paper state NAS Score and supportive measures are necessary for the assessment of NAS with pharmacological treatment only needed if the former fail.
• Did they check to see of their babies were admitted to other hospitals???
• Is it practical to expect that mothers can stay with their babies in most US hospitals?
• Did they consider that costs were decreased because babies were not in the NICU?
What outcomes are enhanced by protocols and quality improvement projects?

One main metric used was length of hospital stay (LOS)
Five studies found significant decreases in LOS
Three studies reported large decreases in LOS with no significance reported
   Asti, 2015, Chisamore, 2016, Hall et al., 2014, Hall et al., 2015,

Another main metric used was length of treatment (LOT)
Three studies found statistically significant reductions in LOT with protocols
   Hall et al, 2014, 2015, Hallet, 2015,

The third metric used was the use of adjuvant therapy
Two of three studies found statistically significant reductions in the use of adjuvant therapy
   Hall et al, 2015, Saunders, 2014
“NAS Assessment and Treatment Protocols are essential for each Neonatal Unit that sees babies with NAS which today is probably most units in rural and urban areas throughout most countries.”

However, it is just common medical sense when dealing with a patient with a specific problem to have protocols. Why should it be different for SUD including Neonatal Abstinence Syndrome?
What have we learned from past and current research that can influence the expression of the signs of NAS?
Summarizing issues that can influence variability in the expression of NAS

- Gestational age—pre-term vs. full term
- Methadone vs. buprenorphine ***
- Maternal nicotine smoking
- Rate of decline of neonatal plasma level of methadone
- Breastfeeding (since 1901!)
- Rooming-In with mother post-partum
- Genetic predisposition and epigenetics
What influence could characteristics of methadone have on NAS severity?
The Challenge of Methadone Dosing in Pregnancy I

• There is significant genetic diversity for the enzymes that metabolize methadone (3A4, 2D6) resulting in different individual metabolic rates (Eap 1999).

• Pregnancy accelerates methadone metabolism. CYP3A is consistently and significantly increased in all stages of pregnancy. (Tracy et al, 2005)

• Absolute clearance of methadone is greater during pregnancy than post-partum (Pond 1985)
The Challenge of Methadone Dosing in Pregnancy II

• *Methadone* elimination is significantly more rapid for pregnant compared to non-pregnant patients (half-life 19 vs. 36 hours). (Jarvis et al, 1999)
• Serum *methadone* dilution and perhaps decreased absorption as pregnancy progresses decreases effective serum levels. (Jarvis, 1999)
Does Dose of Methadone Influence the Incidence and Severity of Neonatal Abstinence?

There is no association between NAS severity and:

- Maternal methadone dose
- Trimester of methadone initiation
- Duration and amount of methadone exposure
- Duration of maternal drug use prior to pregnancy
- No apparent relationship between maternal methadone dose (10-100 mg/day) and frequency or severity of abstinence associated seizures

(Numerous authors: CLEARY, McCarthy, Berghella, Newman, Kandall, Kaltenbach, Herzlinger)
Do Different Dosing Practices Affect NAS Severity?

The fetus is exposed to the serum level, not the oral dose. If methadone is cleared rapidly then the dose can be quite high and yet fetal exposure quite low.

Different dosing practices may effect NAS and partially explain the extreme variability of NAS severity. Rates of RX for NAS in different studies range between 13-93%. (Cleary 2010)
Methadone vs. Buprenorphine


• Numerous reports exist and some randomized clinical trials (gold standard of research) are published, i.e., The MOTHER Study which showed decreased NAS incidence and severity with Buprenorphine vs. Methadone.

• Methadone should be easier and safer for induction because buprenorphine is a partial opiate antagonist (need for withdrawal in the Mother during induction)

• Pharmacokinetics critical to understanding dosing of both medications. Dosed properly, both medications should have low rates of treatment of NAS
Methadone vs. Buprenorphine


• The key to both medications is **constancy of maternal and fetal mu receptor occupancy.**

• Differences in outcomes relate more to **adequacy of dosing, effectiveness of treatment, and hospital NAS management** than to which medication is used, i.e.,
  – McCarthy et al.--29% NAS treatment with methadone
  – Biers et al --82% NAS treatment with buprenorphine.
If maternal withdrawal equates with fetal withdrawal (Kenner and Lott 2007), can maternal withdrawal, or under-dosing, or even single dosing during treatment, sensitize the fetus to withdrawal (Rothwell 2010) or otherwise compromise fetal health, i.e. stress the fetus during development?
The Threat to the Fetus is Opioid Withdrawal, Not Opioid Exposure! I


- Fetal dependence occurs as a normal expected outcome of the transfer of opioids thru the placenta.
- First trimester—the risk to the fetus of maternal withdrawal can be miscarriage.
- Second trimester--the fetal brain has opioid receptors and the capacity for IAS, which shares most of the features of NAS. (McCarthy, JMFWM, 2012)
The Threat to the Fetus is Opioid Withdrawal, Not Opioid Exposure! II


- **Intrauterine withdrawal is a direct threat to fetal health because it is a physical stress that can cause hypoxemia due to reduced placental blood flow and oxygen from uterine cramping and increased oxygen demand from fetal hyperactivity.**

- Fetal brain damage, stroke, and death can occur in severe maternal withdrawal.

- All withdrawal is stressful at any point in the pregnancy for mother and fetus.
Stress is more problematic for the neonate than NAS


- Maternal psychological stress has been shown to have adverse effects on fetal development, independent of any addiction/dependence.
- Maternal stress results in fetal exposure to high levels of adrenalin and corticosteroids which can alter genetic expression.
- Reducing maternal physical and psychological stress COULD reduce symptoms of NAS.
Could Single Doses of Methadone be Problematic for the Fetus? Evidence?

- Significant behavioral abnormalities were found on ultrasound with single doses, i.e., *increased activity before and significant depression after the AM dose*. Ultrasounds normalized on a BID regimen. Are these daily episodes of fetal ‘withdrawal’ causing significant fetal stress? (Whitman and Segal 1991)

- *Fetal cardiac rhythm parameters* were found to be abnormal on single doses but to improve on a BID regimen. (Janssen et al 2011)
The Rationale for Split Dosing

Can more sustained fetal serum levels with multiple daily dosing protect fetal health by preventing problems at both peak and trough serum levels and consequently reduce risks for NAS?

• **More sustained plasma levels** are achieved with **BID dosing** than by **increasing single doses**; This **produces 90% higher plasma trough levels and fewer withdrawal symptoms** in mother and infant (Swift 1989).

• **Increased doses and dose intervals are recommended to compensate for the pharmacodynamic and pharmacokinetic changes in pregnancy.** Jarvis (1999) and Pond (1985)
Summarizing the potential influences of methadone prescribing and the influence on the expression of NAS

- Knowledge gaps concerning methadone pharmacodynamics and pharmacokinetics during pregnancy
- Lack of standardization regarding methadone dosing during pregnancy
- Intrauterine Stress and effects on NAS


Where do we go from here?

• Develop *NAS score with less key items* with feasibility to facilitate easy training;
• Define which *medication for NAS* is best for the treatment of NAS through clinical trials.
• Consider sensitization of the fetus *in utero regarding NAS* and *manage MAT dosing better* –clinical expression of NAS may have more to do with experiences in utero than after birth ***

• *Addiction is a chronic relapsing brain disease* –*Medical doctors need more involvement in the addiction field* to treat the mothers and babies and to contribute to the research in this field.
• Develop *adequate programs in quantity and quality for maternal opioid dependence* providing Comprehensive Services which will produce healthy mothers, healthy babies and decreased fetal stress.
Research dedicated to the fetus and intrauterine abstinence is needed to solve the mysteries of NAS.
There is still a lot that we do not know so research regarding NAS is needed but we must learn from historical accounts and previous studies in order to unravel the puzzles that currently exist for the mother and the baby.
We must remember that the drug exposed baby and his/her mother deserve as much as any mother and baby born in this world…
“You’ve gone a long way baby!” from 1875 with no recommended assessment and treatment and no plausible hypotheses regarding mechanisms, to improved research and clinical practices for mom and baby. The next phase of research will bring the baby with NAS to the 21st Century and beyond!
THE END
Thank you
finnegal337@gmail.com