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Legalization of Recreational Marijuana: Impact of Maternal Use During Pregnancy

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Abstract

Legalization of marijuana for recreational use has increased the overall consumption of Cannabis sativa in Alaska, Colorado, Washington, and Oregon, although marijuana use was already widespread in the U.S. We review the impact of marijuana use during pregnancy and breastfeeding and cite evidence for adverse effects on infant and child neurodevelopmental maturation and cognitive function, as well as epigenetic effects of marijuana exposure on subsequent generations primarily based on animal and limited human studies in fetal brain tissue. Recommendations from several professional organizations which advocate avoidance of marijuana by mothers during pregnancy, and the potential for adverse effects during breastfeeding, are reviewed. Studies find a positive association between parental marijuana and other drug use, and child maltreatment. States with recreational marijuana have enacted laws regarding use of marijuana while driving a motor vehicle; there are existing laws regarding child endangerment which do not specify the impact of marijuana use by parents. As more states legalize marijuana for recreational use, the impact of prenatal exposure to cannabis and infant exposure during breastfeeding need to be carefully documented, with a focus on the relationship between marijuana consumption and outcomes of pregnancy, and infant and child psychomotor and cognitive development. Parenting skills and capacities may be altered with chronic marijuana use and rates of child abuse and endangerment require systematic evaluation and interventions.

Key Words

Marijuana, Δ9 tetrahydrocannabinol, Pregnancy, Breastfeeding, Child Development, Cognitive Development, Parenting Skills, Child Abuse

Introduction

Marijuana (Cannabis sativa and indica) is among the most widely used psychoactive drug in the U.S.A. among women during their reproductive years. Among pregnant women and non-pregnant women, respectively, 3.9% (95% confidence interval [CI], 3.2-4.7) and 7.6% (95 CI, 7.3-7.9) used marijuana in the past month and 7.0% (95%CI, 6.0-8.2) and 6.4% (95% CI, 6.2-6.6) used in the past 2-12 months. During 2013 among marijuana users (n=17,934), nearly daily use was reported by 16.2% of pregnant and 12.8% of non-pregnant women, with 18.1% of pregnant and 11.4% of non-pregnant women meeting criteria for abuse and/or dependence.[1] Metz and Stickrath estimated that the prevalence of marijuana use during pregnancy and lactation ranges from 2-27% depending on the population and method of detection.[2] Twenty-two U.S. states and the District of Columbia have authorized “medical marijuana use;” however, Alaska, Colorado, Washington, and Oregon have legalized the “recreational use” of marijuana for those 21-years and older, although under federal law marijuana use remains illegal (Title 21 United

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"We review the impact of marijuana use during pregnancy and breastfeeding and cite evidence for adverse effects on infant and child neurodevelopmental maturation and cognitive function, as well as, epigenetic effects of marijuana exposure on subsequent generations primarily based on animal and limited human studies in fetal brain tissue."

State Code Controlled Substances Act). Nonetheless, in 2013, 19.8 million individuals reported using marijuana within the last month. The legalization of recreational and medical marijuana use across the United States heightens the potential for increased use among pregnant women. Legalization of recreational use will likely increase the number of fetuses and infants exposed to marijuana in utero, and may increase the number of women who use marijuana while breastfeeding in these states.

Of the known compounds in the marijuana plant, Δ-9 tetrahydro-cannabinol (THC) is one of many cannabinoids such as cannabidiol, cannabinol, tetrahydrocannabivarin, and cannabiogerol known to have pharmacologic effects. These phytocannabinoids are distinct from endocannabinoids that are endogenously produced from arachidonic acid derivatives. Endocannabinoids modulate regulation of movement, memory, appetite, thermoregulation, pain, and immunity through cannabinoid receptors present throughout the body. The endogenous cannabinoid system plays a role in maintaining and regulating early pregnancy and CB1 receptors are present in placental tissue. Stimulation of CB1 receptors in the placenta can impair fetal growth by inhibiting cytotrophoblastic proliferation. The endocannabinoid system plays a major role in embryo survival and brain development. Endogenous cannabinoids and cannabinoid receptors in the developing fetal brain are detected from the earliest stages of embryogenesis and throughout pre-and-postnatal development. CB1 and CB2 receptor mRNA have been detected as early as the preimplantation period in the embryo and in the developing brain prenatal and postnatally.[3] CB1 receptors are identifiable in white matter and cell proliferation region, and are involved in critical neurodevelopmental events such as neuronal proliferation, migration, and synaptogenesis. Endocannabinoids have been shown to regulate neural progenitor cell commitment and survival. The lipophilic properties of cannabis allow it to readily cross many types of cell barriers, including the blood-brain barrier and transplacental membranes. Cannabis and its metabolites have been detected in many human tissues, including the placenta, amniotic fluid, many fetal tissues, and in breastmilk. The concentrations of cannabis and its metabolites can be several times higher than in maternal plasma than in fetal tissue and depends on the amount of cannabis consumed by the mother. Between 1993 and 2008,[4] the mean concentrations of THC in marijuana rose from 3.4% to 8.8%. Recent reports through 2012 reveal concentrations of THC in leaf marijuana up to 12%, and various concentrated preparations and extracts of THC (e.g. "hash oil") contain over 30% THC.[5] Recent reports have also found ammonia levels to be 20 times higher in marijuana smoke than tobacco smoke, while hydrogen cyanide, nitric oxide and certain aromatic amines occurred at levels three to five-fold higher in marijuana smoke.[6]

Marijuana Use During Pregnancy

Cannabis use during pregnancy has the potential to affect fetal development, while the use of THC while breastfeeding during the newborn period may have adverse effects on the newborn. It has been proposed that exposure to cannabis and its metabolites leads to stimulation of the endogenous cannabinoid system that may then disrupt the ontogeny of endogenous endocannabinoid signaling and interfere with synaptogenesis and the proliferation of neural connections.[7] In addition, there is evidence that cannabis may also disrupt developing neutrotransmitter systems such as dopaminergic neurons that are expressed early in the developing brain and exert trophic effects on neuronal cells. Cannabis exposure during pregnancy may down regulate tyrosine hydroxylase activity, the rate-limiting enzyme for dopamine synthesis that has the potential to impact the maturation of dopaminergic target cells. Disturbances in dopamine function have been associated with an increased risk of neuropsychiatric disorders, such as depression, schizophrenia, and drug dependence.[7] Prenatal exposure to THC has been noted to alter endogenous encephalin precursors and the expression of opioid and serotonin receptors in animal models.[8] Δ9-THC, the major active ingredient in cannabis inhibits gonadotropin, prolactin, growth hormone, and thyroid-stimulating hormone release and stimulates the release of ACTH, thereby altering breast milk production in lactating women.[8] Δ9-THC is present in human milk up to eight times that of maternal plasma levels, and metabolites are found in infant feces, indicating that THC is absorbed and metabolized by the infant.[9] It is rapidly distributed to the brain and adipose tissue and stored in fat tissues for weeks to months. Its half-life ranges from 25-57 hours and may be present in the urine for 2-3 weeks, making it impossible to determine those who are occasional versus chronic users at the time of delivery by urine toxicology screening.[9]

Other toxicities related to marijuana use include the direct and sustained inhalation of unfiltered marijuana smoke as opposed to tidal inhalation generally used when smoking tobacco. Exhalation of marijuana smoke poses similar threats to infant health as does secondhand tobacco smoke, which is associated with increased rates of respiratory illnesses during childhood, including: asthma, bronchitis and pneumonia, and more frequent ear infections.[10]

Data on the effect of cannabis use in pregnancy on different birth outcomes have not found an increased risk of spontaneous abortions. However, recent studies suggest that cannabis use during pregnancy is associated with adverse birth outcomes, including: stillbirth, preterm labor, intrauterine growth restriction, and an increase in birth defects. The National Institute of Child Health and Human Development Stillbirth Collaborative Research Network reported that cannabis use is associated with increased risk of stillbirth [odds ratio 2.34; 95% confidence interval (CI) 1.13-4.811].[11] After controlling for tobacco smoking, alcohol consumption, and the use of other drugs, Minnes and coworkers found that cannabis use during pregnancy was associated with low birth weight [odds ratio 1.7; 95% CI 1.3-2.2], preterm labor [odds ratio 1.5; 95% CI 1.1-1.9] small for gestation age

by birth weight [odds ratio 2.2; 95% CI 1.8-2.7), and Neonatal Intensive Care Unit admission [odds ratio 2.0; 95% CI 1.7-2.4].[12] The Generation R study from the Netherlands[13] enrolled over 7,000 mothers and fetal growth was followed using ultrasound during all trimesters and the early newborn period. Maternal cannabis use during pregnancy was associated with fetal growth restriction during the second and third trimesters, and infants were delivered with lower birth weights, with cannabis-exposed infants having a growth reduction of -14.4 gm/week (95%CI -22.9-5.9, p>.001) and reduced head circumference of -0.21 cm/week (95%CI -0.42-0.02 cm). Compared to unexposed infants, this was more pronounced than fetal growth restriction associated with maternal tobacco smoking. Rates of birth defects have been reported to be higher than expected among women using marijuana during pregnancy (obstructive genitourinary defects, polydactyly, syndactyly, and upper limb reduction deformities);[14] however, recent studies have found no increased risk for birth defects.[15, 16]

Disturbances in neurobehavioral function among infants exposed to THC such as exaggerated and prolonged startle reflex, increased hand-mouth behavior, high-pitched cry, poor habituation and disturbances in infant sleep-wake cycles have been reported among babies whose mother revealed cannabis use during the third trimester.[3,17] Evidence suggests that in utero cannabis exposure has an adverse impact on longer-term neurodevelopmental outcomes of exposed infants.[18] Reports of delayed acquisition of visual-perceptual tasks and language skills, increased levels of aggression, poor attention skills, deficits in reading, spelling, and problem solving skills and tasks requiring visual memory, analysis, and integration have been reported in cannabis-exposed infants during later childhood.[19,20] Poorer school performance, as early as 6 years, appears to persist beyond late childhood. Moderate cognitive deficits after marijuana use during pregnancy are found at 4 years of age.[20] There is moderate evidence for association with decreased IQ scores, reduced cognitive function, depression and decreased academic ability in adolescence.[21-23] First trimester marijuana exposure is also associated with poorer reading and composition scores on the Welscher Individual Achievement Test at 14-years of age.[24] There is compelling evidence for an association with attention problems in infancy, among children in pre-school, and childhood,[25-27] and mixed evidence for an association with newborn behavioral issues[28-29] after marijuana use during pregnancy. There is limited evidence for an association with increased depression symptoms and delinquent behaviors and lower 'executive function' for 9-12 year-olds after prenatal marijuana exposure.[28,29,30] Mothers who smoked marijuana during pregnancy also describe their children as more impulsive or hyperactive.[31]

Marijuana and Breastfeeding

Marijuana use during breastfeeding has been associated with delayed infant motor development at one year, lethargy, less frequent and shorter feedings, and high milk-plasma ratios of THC have been reported in "heavy" marijuana users.[32] Δ9 THC is present in human milk up to eight times that of maternal plasma levels, and metabolites are found in infant stools, indicating that THC is absorbed and metabolized by the infant.[33] Δ9 THC is highly lipid soluble and is distributed to the brain and adipose tissue where it is stored for weeks to months. Based on studies in lactating monkeys receiving 2 mg of THC daily, 0.2% of the maternal dose was measured in breast milk over a 24 hour period.[34] Friguis and coworkers document that infants ingest approximately 0.8% of the maternal dose/kg from one "joint" during one breastfeeding and infant may breast feed up 8 to 10 times daily.[35] The half-life is 20-57 hours and stays in the infant's urine for up to 2 to 3 weeks, making it difficult to determine the occasional versus a chronic THC user at the time of delivery by urine toxicology studies.[36] Marijuana exposure from maternal milk during the first month after birth was associated with a decrease in motor development at one year; however, there was no association between marijuana exposure during the third month after birth and motor development.[37,38] The potency of Δ9 THC in cannabis currently available for medicinal or legal use is many fold greater than that used in previous studies.[39] Ongoing evaluation of the impact on infant development in breast-fed infants exposed to currently available marijuana potencies are warranted, especially in mothers using moderate or heavy amounts of marijuana. Miller has summarized the adverse effects of marijuana use on breastfeeding to include: increased tremor, poor sucking reflex, decreased feeding time, slow weight gain, change in visual responses, and delayed motor development. She stresses that marijuana use while breastfeeding is a cause for concern among lactation consultants and medical providers and requires individualized assessment, plan of care, and follow-up of infants exposed to marijuana while being breastfed.[40]

The Academy of Breastfeeding Medicine (www.bfmed.org) advocates that breastfeeding mothers should be counseled to reduce or eliminate their use of marijuana to avoid exposing their infants to the substances in cannabis and of the possible longer-term adverse neurodevelopmental effects from continued use.[41] These specific recommendations can be summarized:

1. Counsel mothers who admit to occasional or rare use to avoid further use or reduce their use as much as possible while breastfeeding, advise them regarding the possible long-term neurobehavioral effects, and instruct them to avoid direct exposure of the infant to marijuana and its smoke.
2. Counsel mothers found with a positive urine screen for THC to discontinue marijuana use while pregnant and counsel them as to the possible long-term neurodevelopmental effects of marijuana exposure.
3. When advising mothers on the medicinal use of marijuana during lactation, that consideration and counseling be given on the known benefits of breast feeding versus the potential risks of exposure of marijuana on infant development.
4. The lack of long-term follow-up data on infants exposed to varying amounts marijuana via human milk, coupled with concerns over negative neurodevelopmental outcomes in children with in utero exposure, should prompt extremely careful consideration of the risks versus benefits of breastfeeding in the setting of moderate or chronic marijuana use and that abstinence from any marijuana use is warranted.

The Academy of Breastfeeding Medicine urges caution but also states that data are not strong enough to recommend against breastfeeding with any marijuana use.

The American College of Obstetricians and Gynecologists (www.acog.org) states: "There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged."[42]

The American Academy of Pediatrics recommends that women using marijuana not breastfeed their infants.[43] Marinol® (Dronabinol) is not recommended in nursing mothers by the manufacturer;[44] the packet insert of Cesamet® (nabilone) also recommends against its use in nursing mothers.[45]

Marijuana and Epigenetic Modifications

Epigenetic modifications of histones play a major role in epigenetic regulation; histone acetylation, methylation and phosphorylation have been implicated in gene regulation and neurobiological disturbances related to drug use during pregnancy.[46] Exposure to cannabinoids during one generation has been implicated in epigenetic changes in offspring primarily in animal studies, although data from humans is emerging. After prenatal cannabinoid exposure, rats self-administered more heroin, particularly when stressed, revealing

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greater opiate reward behaviors than unexposed rats.[47] Studies of prenatal THC exposure in rats have found disturbances in histone modification in the adult brain, and a reduction in mRNA transcript levels in the nucleus accumbens in fetal tissue of cannabis exposed women suggesting that maternal cannabis use alters the developmental regulation of mesolimbic dopamine receptors.[48] Maternal THC exposure during pregnancy has been associated with fetal changes in mRNA expression of cannabinoid, dopamine, and glutamatergic receptor genes in the dorsal striatum key neuronal pathways mediating compulsive behaviors and reward sensitivities.[49] These findings suggest that parental germline THC exposure leads to cross-generational disturbances in the dorsal striatal synaptic plasticity. Paternal marijuana use has also been reported in two-case controlled studies to increase the risk of membranous ventricular septal defects in their children.[50, 51]

Marijuana and Public Health Agencies

Recent reports by public health authorities in Colorado[52] and Oregon[53] have summarized peer-reviewed evidence regarding maternal marijuana use and health effects on infants and conclude the following:

1. THC is present in the breast milk of women who use marijuana and can be detected after recent use.
2. THC is absorbed and metabolized by infants ingesting breast milk of mothers who use marijuana. In one feeding, the exposed infant would intake 0.8% of the weight adjusted maternal intake of one joint and exposed infants will excrete THC in their urine for 2-3 weeks.[35]
3. Although the Colorado report states that there is mixed evidence for an association with motor development in exposed infants, the Oregon report mentions decreased motor development at one year of age. Infants demonstrate signs of reduced muscular tonus and poor suckling whose mothers used marijuana during pregnancy.

The Colorado report states that there is "insufficient evidence that infant exposure to marijuana smoke is associated with Sudden Infant Death Syndrome."

A Washington state document summarizes that "the main psychoactive component in marijuana (THC) passes from mother to child during pregnancy and through breast milk.[54] Emerging research also suggests there is an association between marijuana and decreased fetal growth, development and executive functioning and mood disorders in children. THC stays in the body of mothers and babies for a long time, babies can test positive for THC weeks after being exposed. Babies exposed to THC can have problems with breastfeeding." This report also states "parental substance use doesn't necessarily result in child harm or neglect."[55] If a mandated reporter has reasonable cause to believe that a child has suffered child abuse/neglect they are required to report. New language has been added: "If you (a mandated reporter) believe that a parent's substance use/abuse is causing child abuse or neglect, consult Child Protection Services (CPS). This includes the use of marijuana and alcohol."

Marijuana and Parenting Skills

An issue yet to be resolved by Public Health Authorities or Child Protection Services agencies whose legislative mandate is to protect the care and welfare of children is the degree to which "parenting skills" may be impaired by marijuana use, and what level of marijuana use constitutes child endangerment.[56]

Prenatal substance exposure is associated with a 2 to 3 times increased risk of subsequent child maltreatment.[57]
Among multiple risk factors identified in research literature, family substance abuse is the strongest predictor of child neglect.[58]

In a telephone survey of 3,023 respondents living in 50 mid-size California cities, individual level data on marijuana use and abusive and neglectful parenting were collected. Within one year of the survey, current marijuana users self-identified an increased frequency of child physical abuse but did not self-report physical or supervisory neglect after controlling for parent income, employment and education. Noteworthy, the density of medical marijuana dispensaries and delivery services was positively related to frequency of child physical abuse.[59] Concern has also been expressed because of the wider availability of marijuana "edibles", often packaged in colors and preparations attractive to children. Parents who inadequately supervise and/or underestimate the impact of marijuana ingestion, put their children at significant risk of harm by allowing access to marijuana.[60]

States that have legalized recreational marijuana have enacted statutes regarding child neglect and endangerment. Colorado Revised Statute 19-3-102 defines a baby testing positive at birth for Schedule 1 substances (including recreational or medical THC or other drugs) as an instance of child neglect, which requires a report to social services (C.R.S. 193-102). Colorado and Washington laws specify that drivers with five nanograms/ml of active THC in their blood are considered to be driving under the influence, and that it is illegal to use marijuana in a vehicle. The Colorado Department of Public Health and Environment states, "it is not safe to drive a car while high. Do not let your baby ride in a car if the driver is high." Oregon statutes indicate having a child in the car while driving under the influence of marijuana may be interpreted as neglectful parenting. Smoking tobacco, "weed, plant, regulated narcotic or other combustible substance" with children in the car is a Class D traffic violation according to Oregon Revised Statute (O.R.S,) 811.193. O.R.S. 419B.504 indicates that the rights of the parents may be terminated provided by statute if the court finds that the parent or parents are unfit by reason or conduct or condition seriously detrimental to the child or ward and integration of the child or ward into the home of the parent or parents is improbable within a reasonable time due to conduct or conditions not likely to change including addictive or habitual use of intoxicating liquors or controlled substances to the extent that parental ability has been substantially impaired. Within the legal framework, the degree to which addictive or habitual use of marijuana substantially impairs parenting skills, has yet to be determined.

Present evidence documents that marijuana use during pregnancy has substantial adverse effects on fetal development and neurobehavioral effects from the neonatal period to adolescence. However, limited information regarding the impact of marijuana use exclusively during breastfeeding is insufficient to verify that use of marijuana solely during breastfeeding adversely affects newborns. Lactating women should be counseled that marijuana use is discouraged, based on current evidence. Driving after marijuana use may impair drivers and increase motor vehicle collision risk.[61] Driving with a child in the car, while under the influence of marijuana or other drugs or alcohol is considered child endangerment.

Ongoing surveillance will be necessary to determine whether the legalization of marijuana in greater numbers of infants and children endangered by parents' marijuana use: associated with driving; and through the increase in the prevalence of neglectful or abusive parenting.

Brook and coworkers[62] assessed effects of the interrelationship of mothers' and fathers' tobacco and marijuana use with personality attributes and child-rearing behaviors. In the longitudinal study, 258 parents were seen four times over a 13-year period during their early teens into adulthood. Their findings suggested that parent protective personality characteristics were offset by substance use and resulted in less adequate parenting skills. In a recent study reported from Colorado, Thurstone et al[63] found that among parents using medical

marijuana 6/11 parents reported that using marijuana helped them to be calmer with their children and to manage difficult emotions related to parenting; however, most parents did not want their children to use marijuana, and that these parents sought alternative strategies for managing difficult emotions related to parenting.

Accidental ingestion of marijuana by children is a growing concern because of the increased availability of attractive "edible" forms of marijuana such as baked goods, candies and soft drinks, as well as highly concentrated marijuana resins and extracts (i.e., "hash oil").

Among states with the legalization of medical and recreational marijuana, there has been a marked increase in toxic marijuana exposures of young children.[64,65] Clinical symptoms among children include stupor, vomiting, hypotonia.[66,67] Medical intervention involved multiple tests, procedures, imaging and hospitalization.[67]

Emergency medical responders, emergency room physicians and pediatricians will need to have a high index of suspicion when encountering young children presenting with these signs and symptoms, testing for the presence of THC in the urine, even in the absence of a clear history of marijuana ingestion.

Summary

Legalization of recreational marijuana use by adults of 21 years or older may have anticipated effects on their children requiring intervention by pediatricians, psychiatrists, and teachers. Consideration of the known impact of marijuana use during pregnancy is critical when evaluating children who have developmental delay, inattention, impulsivity, hyperactivity, and externalizing behaviors such as mood/anxiety disorders who present in later years for pediatric, behavioral or educational evaluations. Among risk factors for child neglect, family substance abuse was the strongest predictor of child neglect and an inadequate home environment. Accidental ingestion of marijuana products has been shown to endanger children and greater awareness of the need to test children for THC will be necessary where there is greater access to marijuana and derivative products.

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Author Commentary

Legalization of recreational marijuana has been promoted as a revenue bonus to Colorado (15% excise tax and cities or counties may impose additional taxes). With medical marijuana excluded, Alaska taxes marijuana sold at $50/ounce. Washington state charges a 37% tax on sales. In Oregon, a 25% tax will be imposed in 2016 on recreational marijuana sales. Off-setting these budgetary windfalls will be additional anticipated medical and special educational costs for caring for an increased number of low birth weight infants, neurodevelopmental assessments of children adversely affected by marijuana use during pregnancy, medical costs to treat accidental ingestion, diagnostic costs for behavioral assessments and treatment by pediatricians, psychologists, and mental health providers. Hopefully, a portion of these new revenues will be targeted for research into the long-term medical and special educational needs given that a significantly larger cohort of infants and children will be exposed to marijuana use during pregnancy, lactation, second-hand marijuana smoke and other forms of cannabis ingestions. Higher potency inherent in a commercial product may be tied to a higher risk. State policymakers have an opportunity to direct funding to meet this gap by providing for youth interdiction programs aimed at education and prevention of underage use, as well as research and funding for special education programs for children with special needs.

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Comprehensive Family Support in NICUs

By Sue Hall, MD

Members of the NPA write a regular column in *Neonatology Today*.

Providing comprehensive family support to families whose babies are in the NICU should be a standard of care in all Neonatal Intensive Care Units (NICU). Comprehensive family support goes beyond just "allowing" parents to "visit" their baby and keeping them informed of the baby's medical status. First, it requires recognizing, acknowledging and even normalizing the fear, guilt, and lack of control that parents feel once they are catapulted into the NICU with their sick or premature baby, as well as acknowledging the unsettling disruption of the parent-infant bond they experience and working to repair it. Second, it requires that all staff that work in perinatal service areas (High-Risk Obstetric Clinics and wards, Labor and Delivery, NICU, and NICU follow-up services) understand NICU parents' increased risks for postpartum depression,[1-3] posttraumatic stress disorder,[4-6] and anxiety disorders[2-3] and together provide an integrated continuum of support from the antepartum period through to the post-NICU discharge period to mitigate these risks. And third, it requires that neonatologists collaborate with an interdisciplinary team towards a common goal of providing this support, and that neonatologists are also cognizant of the team's own need for mutual support in this highly stressful work.

In January 2014, the National Perinatal Association (NPA) convened a broad group of approximately 50 people devoted to the well-being of NICU babies, parents and families— physicians (both neonatologists and obstetricians), nurses, nurse practitioners, nurse midwives, developmental care specialists, psychologists, social workers, public health experts, parent support group leaders and parents—to develop interdisciplinary guidelines for psychosocial support services for parents whose infants are hospitalized in NICUs. This group gathered with the common goal of improving the level of psychosocial support provided to NICU parents as well as improving training and support for those who provide care in NICUs. The group was responding to the personal stories of former NICU parents and to the body of literature that demonstrates the increased occurrence of perinatal mood disorders in NICU parents compared with parents of term infants and the adverse impact these conditions can ultimately have on infant development.[7,8]

The workgroup consisted of representatives of 29 professional groups and parent groups and 22 academic institutions. Six interdisciplinary committees, each of which included former NICU parents, worked to produce recommendations in the following areas:

- family-centered developmental care,
- peer-to-peer support,
- mental health professionals in the NICU,
- palliative and bereavement care,
- follow-up support, and
- staff education and support.

The committees gathered research citations and communicated by e-mail and phone to determine evidence-based needs of NICU parents as well as best practices. Many members attended a summit in 2014 in St. Louis, MO, to formulate final recommendations.

Whenever possible the recommendations came from research citations as well as recommendations of other professional organizations such as American Academy of Pediatrics, National Association of Neonatal Nurses, and the National Association of Perinatal Social Workers. Some with a more modest evidence base simply seemed like "the right thing to do."

The recommendations and explanatory narratives were subsequently published in a Supplement to the December, 2015 issue of *Journal of Perinatology*.[9] Twenty-nine professional and parent organizations have now indicated their agreement with the overall tenor of the recommendations;[10] their expressed support does not necessarily indicate agreement with every recommendation, nor does it indicate official guidance from the supporting organization. To help implement the recommendations, the NPA has developed a website for both parents and professionals at www.support4NICUparents.org.

Many individual NICUs and Quality Improvement Collaboratives, such as the Vermont-Oxford Network, have already embarked on initiatives to increase both parent participation in neonatal care and parent support. The NPA's recommendations provide an interdisciplinary and comprehensive viewpoint and add to the body of work offering guidelines for how NICUs can be transformed to further embrace families and promote their well-being. Evidence strongly suggests that by supporting families, we are also supporting improved outcomes for babies. It is the hope of the NPA workgroup that psychosocial support of both NICU parents and staff will be goals equal in importance to the health and development of babies in every NICU.

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Clinical Trials and the Parent Perspective

By Laura B. Martin; Christa D. Terry

Most parents of preemies know that surfactant (a substance that keeps air sacs in the lungs inflated) helps premature babies breathe, but far fewer know that clinical trials helped make surfactant part of standard preemie care.

Graham's Foundation recently collected data directly from 194 mothers and fathers of preemies in seven different countries* to learn more about parents' understanding of and opinions about clinical trials. Of those who participated in the survey, 74% had never taken part in a clinical trial, though 47% understood that clinical trials are an important part of medical advancement, and would feel good knowing they are contributing to the overall development of neonatal care.

Eighty-five percent of those who answered the survey reported they would be more inclined to participate in a clinical trial if they better understood the history of clinical trials and how they have contributed to the outcomes of preemies today. And 8% reported that talking to others outside the Neonatal Intensive Care Unit (NICU) would help them better understand the clinical trial, and help them make an educated decision about participating.

An overwhelming 93% of participants said they would be inclined to participate in a clinical trial if they knew their baby's chance of survival wasn't impacted by the clinical trial, but their long-term outcome would be improved. Seventy-eight percent felt that clinical trials are risky, although 92% understood participants may withdraw from a clinical trial at any time.

More telling was the result of the information gathering we did prior to conducting the survey. Our goal was to speak to at least one parent whose preemie had participated in one or more clinical trials, and while we eventually connected with Holli Olbrich, most of the other parents who responded to our initial query did not even know what clinical trials actually were.

Holli, a nurse who has worked at large university hospitals, shared her experience as a mother of a preemie, Justin, who participated in multiple clinical trials.

Graham's Foundation: What kinds of trials did your preemie participate in?

Holli: "Justin participated in a clinical trial for a supplement to help develop the eyes. It was used to see if it would prevent the development of Retinopathy of Prematurity (ROP). Justin still needed laser eye surgery due to his ROP developing to Stage 3 with plus disease. It was a double blind study, so we do not know if he received the supplement or a placebo. The only difference for Justin's care in this trial was that a second ophthalmologist had to examine his eyes before the surgery and agree with the first doctor's findings."

"We also participated in a double blind study using hydrocortisone to help come off the vent. This was used on babies who were still on the vent after 4 weeks. We don't know if Justin got the medication, but he weaned great from the vent after receiving it. He even was successful on Continuous Positive Airway Pressure (CPAP) for 2 days, but in the end, he needed his Patent Ductus Arteriosus (PDA) ligated. We did this before he would have been given dexamethasone to try and get him off the vent. In the end, his PDA ligation is what helped the most, but at the time he had to recover from two infections before he could be ligated."

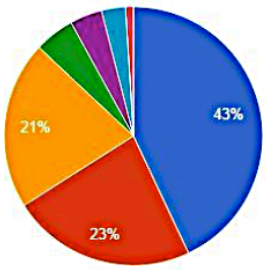
"We also participated in a blood transfusion study. The baby was either on a low threshold or high threshold for transfusions. Justin was in the low threshold, meaning he was not transfused until his hemoglobin was below a certain number (the number changed as he became older). This study led to the attendings and I having some conversations as I was impatient when I noticed his vital signs changing, and felt he needed to be transfused. If I had a good reason for wanting the transfusion they typically agreed with me, and would write an addendum to why they opted to transfuse before he reached the lower threshold. I always had the option to take him out of the study (which I threatened), but they were always willing to work with me and consider my input. The doctors wanted to keep him in the study and work with me rather than have him taken out of the study."

"We were also in a study on families in the NICU and how well prepared we felt based on several factors. This wasn't a clinical trial, but it was an important part of research into how to better involve families with their babies in the NICU. The hope was that depending on what was found by the study, more money would be allocated to things like meal passes, parking passes, more parent accommodations, and how to better prepare families for bringing their babies home."

Graham's Foundation: How much did you know about clinical trials before having a preemie of your own? Do you think your level of understand**ing** was greater than that of most parents of preemies?

If you had a vote for where you think the greatest need for a "breakthrough" solution would help preemies the most, where would you place your vote?

Retinopathy of Prematurity (ROP)
Prevention and Treatment of Necrotizing Enterocolitis (NEC)
Neonatal Abstinence Syndrome (NAS)
Neonatal Lung Injury
Neonatal Brain Injury for Preterm Infants
Neonatal Sepsis
Other



43% - Neonatal Brain Injury for Preterm Infants
23% - Neonatal Lung Injury
21% - Prevention and Treatment of Necrotizing Enterocolitis (NEC)
5% - Other
4% - Neonatal Sepsis
3% - Retinopathy of Prematurity (ROP)
1% - Neonatal Abstinence Syndrome (NAS)

Nick Hall, Graham's Foundation

Holli: "As a nurse who worked in two large university hospitals, I felt I had a better understanding of clinical trials than most other parents. I had already seen the other side of clinical trials as a nurse. I never imagined I would be asked to have my child be in trials and it was very scary at first."

Graham's Foundation: Were you offered the chance to participate in your NICU or did you find the clinical trials on your own? If your NICU presented the opportunity, what kind of information did they give you? Did it feel sufficient?

Holli: "The NICU we were in did a lot of research. They presented all the information and gave handouts. Any time I had questions, the lead researcher would come and talk about them with me. I was actually asked by a Fellow from the Level 4 NICU nearby if he could come and talk to me about being a parent in the NICU and medical decision-making as a parent. We were given a parent packet on each study that we participated in, and it included who the researchers were and how to contact them if any questions weren't answered. I felt it was sufficient information, but as a nurse, I understood more of what was going on. My husband normally had a lot more questions than me, and at times, he felt overwhelmed by the information being given."

Graham's Foundation: Were you ever worried about the potential negative impact of drugs or treatment on your preemie? What helped you accept the potential risks?

Holli: "Every decision we had to make while Justin was in the NICU seemed terrifying. In the end, it was nice to know that we weren't just helping Justin, but also all the other babies born extremely early. I asked numerous questions and made sure I was at the NICU to discuss Justin's care with those caring for Justin. Working as a team was very important.

Knowing the benefits and the risks helped me decide to participate."

Graham's Foundation: Ultimately, why did you choose to have your preemie participate? What do you think, if anything, might help other parents feel more comfortable allowing their preemies to participate in clinical trials?

Holli: "Knowing that these were the newest options and the risks of remaining on the vent as well as the risk of ROP made me decide to give Justin the best chance and participate. As far as the transfusion study, I felt we would help other preemies if it could be determined whether fewer transfusions led to better outcomes."

Graham's Foundation: Has there been any follow up or information passed on about the clinical trials after your preemie left the NICU?

Holli: "We are still in NICU follow-up period. The team will follow Justin for 2 years. We will never know if Justin received the medications or not, but I'm hoping we will hear the outcome of the research studies."

Why Consider Being a Part of a Clinical Trial

Clinical research has improved children's health outcomes in so many areas, from pediatric cancer treatments to interventions for premature babies, but there is still so much more to learn, and a lot of misunderstanding among those who might benefit from further clinical research. What follows is an outline of parent-focused information designed to help mothers and fathers of preemies understand what clinical trials are, and why they are so vital to bettering future outcomes.

Many medicines, medical devices and treatments that are routinely given to children, including preemies, have not been tested in babies or children. Just to provide perspective, children receive medicines at nearly half of all medical visits but 70% of those medicines have only been tested in adults and some have not even been approved by the Food and Drug Administration (FDA) for use in children.

Infants and children are routinely prescribed medicines and treatments based on what works in adult patients. This off-label use of drugs and devices is frequently effective, but simply adjusting an adult dose is guesswork, not science. This method of treating children ignores the fact that children's brains and bodies are still developing, and that a child's body may simply process medicines and treatments differently.

Studies that focus on improving clinical care in infants and children help researchers develop treatments, drugs, and devices specific to their needs. While it's only natural that parents and caregivers – particularly those responsible for the sickest children – will have questions, concerns and even fears, without research that involves the children themselves there is no way to find the best treatment options for them.

Clinical Trials Can Help

Clinical trials can help in the following way:

- Develop effective treatments for diseases and conditions that occur only in children,
- Develop child-specific treatments for diseases and conditions that manifest differently in infants and children,
- Develop treatments that result in better long-term health outcomes or impact the health of future generations of children,
- Determine the best drug dosages for children to avoid both side effects and under-dosing,
- Develop child-friendly delivery systems for necessary medications, like chewables, liquids or tablets,
- Determine the effects existing medicines and treatments have on children's developing brains and bodies.

One clinical trial currently enrolling preemie participants is Shire's ongoing ROP Study, which is examining whether introducing a medication which replicates a growth factor that is a natural part of the intrauterine environment could prevent ROP. Another upcoming trial being conducted by Nutrinia involves a drug to help promote the growth of the GI tract in preterm infants, allowing them to

What is your general understanding and attitude towards clinical trials?

This is just a way for some company to make a lot of money someday, and my baby is going to be a guinea pig.

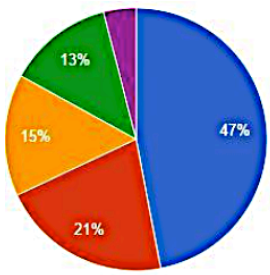
I understand that they manage the risks, and won't suggest we participate if they don't think it could be beneficial.

If needed to help save our baby, then yes, but otherwise, no thanks.

I really don't know that much about them so I need to do a lot of additional research.

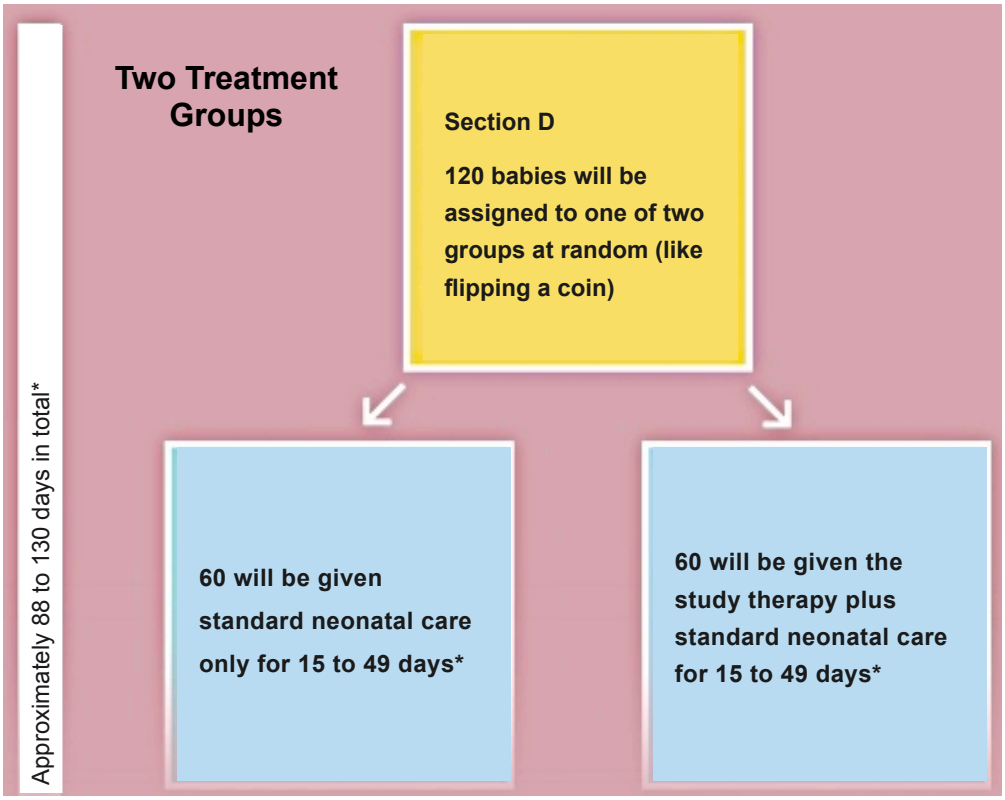
I understand that clinical trials are a necessary part of advancement, and would feel good knowing we are contributing to the overall development of neonatal care.

Fine, if others want to participate, but not my baby.



47% - I understand that they manage the risks, and won't suggest we participate if they don't think it could be beneficial.
21% - I understand that clinical trials are a necessary part of advancement, and would feel good knowing we are contributing to the overall development of neonatal care.
15% - If I need to help save our baby, then yes, but otherwise, no thanks.
13% - I really don't know that much about them so I need to do a lot of additional research.
4% - Fine, if others want to participate, but not my baby.
0% - This is just a way for some company to make a lot of money someday, and my baby is going to be a guinea pig.

Nick Hall, Graham's Foundation



About this study. *Trying to improve vision outcomes. The ROPP-2008-01 clinical study will look at whether a study therapy that contains IGF-1 (among other things) may prevent Retinopathy of Prematurity (ROP) and improve vision outcomes for premature babies. This study is divided into four sections. Data from Sections A, B and C showed the study therapy to be safe and well-tolerated in a small number of very premature babies. So we're ready to move to Section D. This section will assess the study therapy in a larger number of babies.*

better tolerate enteral feedings (www.nutrinia.com/?page_id=2156). If either trial ultimately proves successful, the impact will be huge not only among the preemies in the studies, but among the preemie population as a whole moving forward.

Parents and caregivers of preemies presented with the opportunity to participate in clinical trials obviously need to weigh the risks against the potential rewards, both individually and as part of the larger community of premature infants and children. But recent studies have shown that opting into research (versus taking part in only standard care) is safe.

"'Neonatology is a relatively young field, and many therapies that are commonly used in preterm and sick infants have never been tested,' Dr. Elizabeth E. Foglia from the University of Pennsylvania told Reuters Health."

Researchers at the University of Pennsylvania found that even extremely premature infants who take part in clinical trials don't have worse outcomes than preemies who don't take part in research. Researchers followed 5,000 preemies born between 22 and 28 weeks gestation, and found that those who participated in trials did not have additional complications.

"Neonatology is a relatively young field, and many therapies that are commonly used in preterm and sick infants have never been tested," Dr. Elizabeth E. Foglia from the University of Pennsylvania told Reuters Health. "The only way we can know with confidence that a given therapy works in our patients is by performing well-designed and appropriately regulated randomized controlled trials. These findings demonstrate that the practice of performing randomized controlled trials in extremely preterm infants is not detrimental to trial participants' outcomes."

Footnote: **A significant portion of those who participated were: from the USA, Caucasian, female, married or in a domestic partnership, and between the ages of 25-34.*

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This Article is an Informational Resource for the Parents of Preemies

NEONATOLOGY TODAY has included this article as a good informational resource for the parents of preemies. Since 85% of those who answered the survey reported they would be more inclined to participate in a clinical trial if they better understood the history of clinical trials and how they could contribute to the outcomes of preemies today. To download a PDF of this article to give to the parents of preemies go to: http://www.neonate.biz/GF.pdf

Graham's Foundation is focused on helping parents directly through their care package and mentor programs, Graham's Foundation explores new ways to empower parents of preemies through advocacy and research to improve outcomes for their preemies and for entire families.

To learn more about Graham's Foundation and how you can help, please go to their website: http://grahamsfoundation.org/

Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

New Online Tool Created to Tackle Complications of Pregnancy and Childbirth

Newswise — Mother Nature (aka evolution) has been particularly guarded when it comes to her secrets regarding human pregnancy, which has made it particularly difficult for medical researchers seeking answers to the complications of gestation and childbirth, such as preterm birth, which is the leading cause of infant mortality worldwide.

To lift this veil of mystery, an interdisciplinary team of biologists and medical researchers have created a new platform, which they call GEneSTATION (its name stems from a play on the words "gene" and "gestation"), that is specifically designed to leverage the growing knowledge of human genomics and evolution to advance scientific understanding of human pregnancy and translate it into new treatments for the problems that occur when this complex process goes awry.

The new online resource is described in an article published on Nov. 11th by the *journal Nucleic Acids Research*. It integrates diverse types of "omics" data (genomics, proteomics, transcriptomics, etc.) with life history information on pregnancy and reproduction from 23 species of mammal. These are linked with a number of special clinical databases with information about human-pregnancy-specific diseases.

"Given the importance of the subject, it's shocking that we know so little," said project leader Antonis Rokas, Professor of Biological Sciences at Vanderbilt University.

A big part of the problem has been that no other mammal provides a satisfactory model for human pregnancy and gestation. Researchers who study other human organs – kidney, liver, heart, bone etc. – have generally been able to find animals with organs that are very similar to those in humans. As a result, they have been able to learn a great deal about how the human organs work by studying their animal counterparts.

Although mammals ranging from mice to humans use basically the same organs to nurture pregnancies and give birth, the dramatic differences in the structures of these organs have limited the value of studying other mammals.

"It's something of a paradox," said Rokas. "Although the mode of reproduction is highly conserved in mammalian evolution, several of the organs associated with pregnancy, such as the placenta, are in fact among the most variable."

Furthermore, "pregnancy involves extremely complicated interactions between genetics and environment," added Patrick Abbot, Associate Professor of Biological Cciences at Vanderbilt University and co-author of the study.

The resulting limitations in the scientific understanding of human gestation and pregnancy have emerged as a major obstacle to finding effective treatments for the complications of pregnancy. For example, preterm birth has become the leading cause of death in newborns and in children under the age of five. In the U.S. and around the world today, more than one in 10 of all births are preterm.

Growing recognition of this problem has prompted a number of different funding agencies to begin major research programs in the area. One is the National Institutes of Health's Human Placenta Project. Another is the March of Dimes' Prematurity Research Centers program, "dedicated to solving the mysteries of premature birth."

The origin of the GEneSTATION project was a series of discussions among Rokas, Abbot and Louis Muglia, who was Vice Chair for Research Affairs in Pediatrics at Vanderbilt University Medical Center. Muglia subsequently moved to the Cincinnati Children's Hospital Medical Center where he became the coordinating principle investigator of the March of Dimes Prematurity Research Center Ohio Collaborative, which is supporting the project, where Rokas, Abbot and Ken Petren of the University of Cincinnati are leaders of one of the collaborative's five research themes.

"I'm very excited about the prospect that GEneSTATION represents," said Muglia. "You couldn't have done this ten years ago because the data just didn't exist."

In order to address this problem, Rokas, whose research until recently was centered on the evolutionary genomics of fungi, and Abbot, whose studies focus on understanding the evolution of cooperation, together with Rokas lab postdoctoral research associate Kriston L. McGary, tried thinking outside of the box.

"GEneSTATION is a new way to organize the information and to look at the problem," said Abbot. "We hope that it will allow researchers to use the variability of mammalian pregnancy as a tool to attack problems like preterm birth and we hope it will bring fresh, new minds to study pregnancy-related problems."

An example of how this new platform works is research being conducted by team member Tony Capra, Assistant Professor of Biological Sciences at Vanderbilt.

Capra used GEneSTATION to compare the regions of the human genome that regulate gene activity in the placenta across 20 mammalian species. "In particular, I looked for regions that were conserved in other mammals, but show a large amount of change in humans," he said. "When I shared the results with my colleagues in Cincinnati, they told me that they had independently found that one of regions that I had identified was often deleted in families at high risk for preterm birth!"

Vanderbilt University Medical Center Associate Professor David Aronoff, who directs the Vanderbilt Pre3 Initiative, is an early adopter of the platform. "The availability of GEneSTATION is a major leap forward in efforts to understand preterm birth. It is directly relevant to the efforts of the Pre3 initiative, which is an interdisciplinary group of faculty and trainees with a shared interest in reducing the burden of adverse pregnancy outcomes and prematurity," he said.

"At its core, the development of GEneSTATION is the outcome of a collaboration between four amazingly talented trainees, graduate student Mara Kim, class of 2015 undergraduate Brian Cooper, research assistant Rohit Venkat, and Kris McGary," Rokas said. "Having a world class computing facility on campus also helped," he added, referring to the Advanced Computing Center for Research and Education, where GEneSTATION was developed.

Additional Vanderbilt University team members are postdoctoral research associate Julie Phillips, graduate student Haley Eidem, postdoctoral research associate Jibril Hirbo, and class of 2018 undergraduate Sashank Nutakki. Scott Williams from Dartmouth College is also a member of the team.

Adults Born Preterm at Risk of Early Chronic Disease: New Review Offers Key Pointers for Doctors Treating Such Patients

Premature birth is linked to an increased risk of heart disease, high blood pressure, pregnancy complications and other chronic diseases

in adulthood. A new review in CMAJ (*Canadian Medical Association Journa*l) aims to help physicians identify adults who were born premature to prevent and manage health conditions.

In Canada, 8% of babies are born premature (before 37 weeks' gestation), and more than 90% survive, owing to advances in health care. However, there are no guidelines for long-term management of people born prematurely, who are at higher risk of certain chronic diseases.

"By identifying patients who were born prematurely, we can take steps to prevent and manage chronic diseases for which they may be at risk to help prevent early death and allow a patient to live a longer, healthier life," states Dr. Thuy Mai Luu, staff pediatrician, Division of General Pediatrics, Centre hospitalier universitaire Sainte-Justine Research Center, Montréal, and Associate Professor, Faculty of Medicine, Université de Montréal, with coauthors.

Young adults born preterm have a 40% increased risk of premature death compared with people born at term.

Adverse health conditions associated with preterm birth may include a higher risk of hypertension and heart anomalies associated with heart failure, increased risk of diabetes, including gestational diabetes in pregnant women, impaired respiratory function and suboptimal bone mass that can lead to osteoporosis and fractures.

Recommendations:

- Regular measurement of blood pressure to help manage risk of early heart disease, including monitoring of pregnant women who were born preterm
- Pulmonary function testing for adults born preterm who have long-term respiratory issues
- Calcium-rich diets and weight-bearing exercises to prevent osteoporosis and reduce risk of fractures in adults born preterm
- Consideration of preterm birth as a risk for Metabolic Syndrome.

"It is our role as clinicians to identify patients at risk by enquiring about perinatal history to the same extent that we ask about smoking or family history of early cardiovascular death," the authors conclude.

Hearts and Minds: Study Uncovers Genetic Links

Newswise — Babies born with heart problems have a number of genetic changes in common, even when there is no family history of heart disease, scientists have found.

These babies, who are at risk of going on to develop problems with brain function as well as difficulties with their hearts, could be helped if they were tested and the genetic abnormalities they carry identified. This might lead to interventions that could improve school performance, employability and quality of life, the scientists say.

The work comes from a large consortium based in the US, collaborating with teams in the UK. The researchers, whose results were published in the journal *Science*, studied 1200 individuals with Congenital Heart Disease; that is people who were born with heart problems such as a hole in the heart, or abnormal connections between the heart and main blood vessels. Some had heart problems only. Others had problems with brain function too. The scientists compared their genetic make-up with that of close family members and healthy controls, a process that involved de-coding and analysing the DNA blueprint, or exome, of some 6000 people.

They found several new genes causing Congenital Heart Disease, and also found shared changes in individuals with congenital heart disease and people with developmental problems with brain function.

Though it's been known for a while that some people with Congenital Heart Disease go on to have neuro-developmental problems, it has not been clear how the two are linked, and doctors have not been able to tell which patients will develop problems and might benefit from early help.

Dr. James Ware, co-first author of the paper and Clinical Senior Lecturer in Genomic Medicine at the MRC's Clinical Sciences Centre (CSC) based at Imperial College explained, "One question has been whether these neuro-developmental problems are caused by the heart disease – perhaps due to problems with the blood supply to the brain, either because the connections to the heart are abnormal or because patients undergo complicated heart surgery, including heart bypass, as a baby – or whether the brain function problems and early heart problems are actually part of the same condition. We found that it's all part of the one condition - the same genetic abnormalities are causing both sets of problems."

One of Dr. Ware's key contributions to today's study was analytical software, called "denovolyzer", which analyses whether a specific gene is carrying more "de novo" mutations than might be expected. De novo mutations are those that arise sporadically rather than being inherited. He helped to develop the approach with a team of statisticians led by Professor Mark Daly at Massachusetts General Hospital and the Broad Institute in Boston. He describes it as a powerful new way to interpret genetic variation, and says he hopes this software, which is open source, will help other scientists working on similar problems in medical genetic research.

Dr. Ware did his PhD and a post-doc at the CSC, then spent three years in the Genetics Department at Harvard Medical School in Boston - where he carried out this work in the laboratory of Professors Jon and Christine Seidman. He returned to the CSC from Boston in October to start a new group at Imperial College, working closely with Dr. Stuart Cook, who leads the Cardiovascular Magnetic Resonance Imaging and Genetics group at the CSC. Dr. Ware is funded by a Fellowship from the Wellcome Trust, and is honorary consultant cardiologist at Royal Brompton Hospital.

The U.S.-centered collaborative effort behind today's results included the Pediatric Cardiac Genomics Consortium, Pediatric Heart Network and the Cardiovascular Development Consortium.

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