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IN THIS ISSUE

Assisted Reproductive Technologies (ART) and In-Vitro Fertilization (IVF): Has the Promise Been Realized?

By Mitchell Goldstein, MD;
T. Allen Merritt, MD;
Raylene M. Phillips, MD
Page 1

Applications for a Mobile Life: In Life, Part 3 of 3 Social and Mobile Media for the Neonatologist

By Clara H. Song, MD
Page 9

The National Perinatal Association Facilitates Collaboration to Improve Perinatal Care

By Raylene Philips, MD
Page 10

Medical News, Products & Information

Page 11

Upcoming Medical Meetings

Page 17

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Recruitment Ads: Pages: 3, 5, 13, 15, 18

Assisted Reproductive Technologies (ART) and In-Vitro Fertilization (IVF): Has the Promise Been Realized?

By Mitchell Goldstein, MD; T. Allen Merritt, MD; Raylene M. Phillips, MD

Since the birth of the first infant by in vitro fertilization (IVF) in 1978, IVF pioneered by Drs. Patrick Steptoe and Robert Edwards can justifiably be called one of the major medical breakthroughs of the 20th century.^{1,2} Births after IVF from 1978 to 2003 numbered about one million. By 2005, over 2 million babies, and by the end of 2013, over 5 million babies were born after IVF worldwide.³ In Europe, 2-3% of all births each year result from IVF. On the high end, Denmark and Belgium each report approximately 5% of their births result from Assisted Reproductive Technologies (ART).³

Overall, 1.6% of the 3,953,590 births in the U.S. are from ART procedures according to National ART Surveillance System (NASS) in 2011. Although actual numbers may in fact be under-reported by use of birth certificate data, the numbers are significant. The number of births from ART procedures in the NASS was reported to be 38,496 compared to 18,560 reported on birth certificates using data from 27 states and the District of Columbia.^{4,5}

Reported data reveals that the percentage of births resulting from ART procedures were 2.06 times higher among jurisdictions reporting to the NASS (1.44% of all births) compared with birth certificate data (0.70%).⁵

The dramatic increase in births resulting from ART for subfertility has occurred despite an observational study that showed that 95% of 350 couples planning a first pregnancy conceived within 24 months.⁵ Approximately 50% of all ART births were from women under the age 35 years.^{5,6} The data suggest a lack of confidence among sub-fertile couples and their physicians that conception would eventually occur naturally. The promise of using ART technologies to hasten conception, use of embryo cryo-

preservation of embryos, and now the promotion of “egg freezing” among career-focused or more affluent women during optimal periods of their reproductive life has greatly increased the use of ART.^{3,4,7,8} Further, the widespread availability of IVF services in private fertility clinics with more of a commercial focus has presented ethical challenges.⁹⁻¹¹ Many of these private clinics are at non-academic centers with minimal oversight. These providers often fail to heed recommendations of their professional societies regarding primarily single embryo transfer.¹² Although professional oversight has intervened in extreme cases, this area is still largely unregulated.^{13,14}

IVF was initially developed for women with subfertility secondary to tubal disease; however, the indications for IVF have grown to include other types of subfertility. These may include: endometriosis, unexplained subfertility, the effect of maternal aging on ovarian function, and even mild “male factor” infertility.¹⁵⁻¹⁹ Most recently, IVF indications have broadened to include use of donor eggs for same sex male couples, or donor sperm fertilized eggs from female couples.^{20,21} The use of egg retrieval and freezing among women has

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also expanded to those who may wish to preserve fertility because of required chemo or radiation therapy, or among women seeking to delay pregnancy and child-rearing in pursuit of career goals. However, 88% of the women who freeze their eggs do so because they do not have a partner.²² In the United States, the number of IVF cycles offered annually increased from 90,000 in 2000, to more than 150,000 in 2010, while the number of women with tubal problems as an indication for IVF fell from 25% to 16%.^{3, 23} Although the American Society for Reproductive Medicine has indicated that egg freezing should no longer be considered experimental, there was not enough data to recommend egg freezing for the purposes of delaying childbearing.^{3, 24} The value of IVF in the decreasing number of women with tubal obstruction has been evaluated in a Cochrane review comparing IVF with expectant management in women without tubal problems but with unexplained infertility who had been trying to conceive for an average of 4 years. The trial reported live birth rates of 29% in women randomized to one cycle of IVF versus 1% in the expectant management group. Thus, IVF and other techniques of ART have achieved laudable goals in this particular patient population. However, while IVF reduced the time to pregnancy, it did not alter the pregnancy rates achieved in expectant management group at 24 months.²⁵ The time for optimal intervention with IVF when there is unexplained subfertility continues to remain elusive, as it does with "male factor" infertility.²⁶ Economic modeling studies have found that in younger women with no obvious cause of infertility, IVF is not cost effective within three years of trying to conceive, and is perhaps used indiscriminately without giving natural methods an adequate trial.^{3, 5, 27, 28}

Intervention with ART does not come without risk. Bewley et al. reported in the *British Medical Journal* several ma-

ternal deaths associated with IVF procedures. This data from the United Kingdom were corroborated by data that showed that overall mortality in IVF pregnancies was higher than maternal mortality rate in the general population in the Netherlands. There were 42 maternal deaths/100,000 IVF pregnancies compared to 6 deaths per 100,000 pregnancies in mothers with natural conception.²⁹

There are risks for babies conceived with ART as well. Infants delivered after ART and assisted insemination fare worse than naturally conceived infants. Higher rates of prematurity and low birth weight can lead to prolonged stays in Neonatal Intensive Care Units.^{24, 30-32} These complications occur at enormous cost compared to infants conceived naturally and born at term. Roughly 37% of ART births were delivered at less than 37 weeks. Approximately one third were both low birth weight and premature. Multiple births accounted for 48% of all births after ART. Multiple birth has been shown to substantially increase the rise for neonatal illness, and thus, the requirement for neonatal intensive care.^{4, 6, 30-33} Both premature birth and at low birth weights have documented risks, and may be associated with life-long morbidities.^{29, 32}

In addition to increased risk for multiple gestation pregnancies, premature birth, and low birth weight, higher rates of birth defects have been noted in carefully conducted surveillance studies performed in Western Australia and Europe.³⁴ Using California data, similar adverse outcomes for infants delivered after ART or AI procedures have been documented.³⁵ Otherwise "healthy" children born after IVF have higher blood pressures, increased adiposity and glucose levels, and more generalized vascular dysfunction than naturally conceived children.²⁴ Epigenetic alternations in the genome of infants born after certain ART techniques have also been documented.³⁶



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The National Perinatal Association has emphasized in published guidelines that:³⁷

1. Prospective parents should receive informed consent prior to considering ART. While it has been argued that infertility itself bestows some additional risks of prematurity and birth defects, it is evident from large studies that ART adds cumulatively to these risks.
2. Prospective parents should receive pre-conceptual counseling from a multidisciplinary team prior to the initiation of ART procedures, and take part in a thorough discussion of the potential emotional and economic costs of having a premature and/or low birth weight infant or an infant with a higher risk of birth defects. Grief counseling should also be available to address issues related to infertility as well as the high likelihood of procedure failure.
3. Pregnant women using ART should receive comprehensive obstetric care that includes access to specialists in Maternal-Fetal Medicine. Access to a Neonatal Intensive Care Unit should be part of the delivery and birth plan. These women should be informed of the potential risks of Ovarian Hyperstimulation Syndrome, including the possibility of ascites, pulmonary edema and even death.
4. Insurance companies should pay for evaluations of women and men presenting with infertility and present alternatives to the use of ART technologies.
5. Insurance companies should pay only centers that adhere to professional guidelines and standards published by the Society for Assisted Reproductive Technology by centers seeking third-party payment. Insurance providers should include a preference for single embryo transfer.
6. Third party payment should reimburse for services provided by providers and Fertility Centers that report their results to the Centers for Disease Control and Prevention, and such reports should include the number of pregnancies per patient, number of cycles of IVF for a pregnancy with a life birth, infants born per cycle, and infant birth weights, gestational age, and birth defects. Neonatal morbidities associated with prematurity and/or low birth weight should be included in the reporting requirements of the CDC.
7. Surrogate pregnancies resulting from IVF should occur only after contractual arrangements obtained prior to in vitro conception and prior to embryo transfer. Ideally, the procedures for legalization of the intended parents should be within the same jurisdiction because of the legal requirements that vary between jurisdictions.
8. Medical "tourism" for the use of international surrogates should be discouraged, as it may be viewed as exploitation of women in other countries. In these situations, the medical record may have to be very

carefully framed to avoid placing the parents at risk for criminal prosecution upon return to their home county.

9. "Egg donation" for purposes of delaying reproduction requires substantial research to determine the impact of prolonged egg storage and successful pregnancy outcomes in the future. Women undergoing oocyte donation should receive low dose stimulation regimens and should not be stimulated with higher doses in order to obtain more eggs than would be expected during a standard IVF cycle. There is no evidence that obtaining large numbers of oocytes is beneficial and all women receiving ovarian stimulation, whether for their own IVF or as an oocyte donor, should receive the lowest effective dose of gonadotropins. Hyperstimulation has been shown to increase the risk for complications.^{38, 39}
10. State regulatory agencies that license and provide oversight for the collection of human tissues should provide the same level of oversight for sperm banks as they do for clinics that perform egg retrieval and the freezing and/or "sale" of collected oocytes for use by others.

The National Perinatal Association recognizes the advocacy for the well-being of women as extensively documented in "Our Bodies, Ourselves" and others who present a more balanced evidence-based information source for women considering delayed reproduction by relying on the technologies associated with ART and are focused on achieving safe outcomes.^{37, 40} The National Perinatal Association understands that personal and professional pressures, as well as, life circumstances contribute to the complex decision by many women and men to choose to reproduce later in life. However, medical professionals have a fiduciary duty to begin to discuss fertility preservation early during an adult's life and assist in providing current information regarding all options regarding childbearing.^{3, 11, 41, 42} It is the ethical responsibility of physicians and society to provide currently available alternatives, and offer support to those experiencing these life crises. As echoed by a leading authority on IVF, Dr. Eil Adashi, former President of the American Gynecological and Obstetrical Society, "alleviation of barrenness [is] a laudable goal....multiple gestation challenge by its very nature is a public health issue," and "our ultimate, if not immediate goal is clear: healthy singleton births."⁴³

Societal expectations have changed since The Second World War, which forced many women into the workplace, and into roles that had traditionally been male dominated (e.g., Rosie the Riveter). Although the expectation was that these women would go back to their traditional roles once the war was over, the idea that a woman had no place in the workforce was forever quashed. They assumed the full benefit, as well as the risk.⁴⁴

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The woman's rights movement of the 1960's emphasized the right of women to have a life outside the home that was distinct of the distaff hoisted on them by society. Modern conveniences such as the dishwasher, washing machine and dryer, and central heating lightened the workload at home for many women. Safe birth control and reproductive planning was available. A woman could have control of her environment and her body. Her right to choose her life's path outside traditional roles was increasingly accepted. Female gender was not an impediment to success in the career world.⁴⁵

There were other considerations as well. Infant Formula was promoted as "safer" and more "nutritious" than ever before. Breastfeeding was dismissed as "old fashioned" and "dirty." Pediatricians actually begged mothers not to consider breastfeeding their babies. Having a baby no longer meant having to commit to months or even years at home breastfeeding. The feminist movement embraced this and emphasized that a woman could truly have it all. With a four to six week childbirth leave a couple of times during a lifetime, a woman could have both family and career.

The aforementioned novel fertility technique developed by Patrick Steptoe and Robert Edwards in the mid 1970's changed everything once again. Although ethicists and moralists initially debated the utility of the procedure later to become known as IVF (in vitro fertilization) and questioned whether the improved outlook for fertility justified the cost and potential complications, Dr. Edwards was awarded the 2010 Nobel Prize in Medicine for this work.^{1, 2} Increasingly it was possible not only to minimize the time off for childbirth, but also to minimize the chance that the birth would occur during a time that was likely to interfere with career advancement. Women were truly "liberated" to conceive on their own terms.

Beyond the technical aspects, we have lost something else. In the pursuit of the perfect career, family architecture, and time, the idea of what is "normal" has shifted. Although being a good mother is perhaps the highest form of "success," increasingly, more women are foregoing the optimal period of time in life when childbearing is least risky and presents the fewest complications for mother and baby. Never mind the fact that we have the technology to produce a viable pregnancy in a 60-year old woman with the semen of her son and the ova of her daughter in law, is it the right thing to do? Beyond health considerations, what about a child's right to have an adult who is able to parent them? Although it may be reasonable for a 40-year old to provide the care for a newborn baby and be financially and emotionally responsible to raise the child, what age is the appropriate cut-off? Even if it were assumed that most of us reach a life expectancy of at least 75, many do not. Will the daughters of these more senior parents have to increasingly drop out of high school and forego college to provide elder care? Will they too be forced



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into the cycle of deferring fertility because of the demands placed on them financially and emotionally by their aging parents?⁴⁶

Perhaps we only need to look to Europe to see that our best efforts may be ill conceived. Certain countries in Europe are faced with a birth rate that is declining so fast as to put their economy in jeopardy.⁴⁷ Without significant immigration, re-establishing the number of births has become a national priority.⁴⁸⁻⁵⁰ Generous maternal and paternal leave are commonplace. The four to six weeks that has become the standard here in the United States pales in comparison to the 480 days allowed for combined parental leave in Sweden. Many European countries actually reward pregnancy beyond a simple deduction on the income tax form.^{51, 52}

Although the need for ART is clear, reproductive freedom should not be about conforming to a societal expectation that has focused on achieving a “biological” revolution by forcing women to forego a natural pregnancy at an earlier age in order to maximize her potential in the career world. The increasingly popular notion that ART can be used to replace normal conception is flawed. In the same way that the medical profession has rediscovered the importance of breastmilk, we should instead focus on encouraging what is physiologically more appropriate, resetting our expectations, and changing our social norms so as not to punish women economically or professionally for wanting to conceive naturally, at a physiologic time that is safest for themselves and their babies.

Although IVF was started with noble aims to assist women with subfertility, much of the current wave of expansion is unwarranted and, indeed, over-sold. Fertility clinics promoting IVF, egg freezing, and other assisted reproductive technologies too often create an unwarranted market and scientifically unjustified “demand” for these services. With time, a certain percentage of these women would be able to conceive naturally. “Egg Freezing Parties,” a current trend in promotion of egg freezing and storage, are hyped by some clinics and financiers to promote these services, yet often fail to inform women the true likelihood of having a healthy live-born child. These expensive procedures, that pose a significant risk for the women involved, may have success rates of as low as 2-12%, but up to 47.1% from cryopreserved oocytes used to create embryos that is much less than 56.1% with fresh oocytes [p<.001].^{53, 54} In these situations, Assisted Reproductive Technologies are misused and, as such, fail to meet the criteria for the medical axiom of “first do no harm” or *primum non nocere*.

As health professionals in the field of perinatal medicine, it is our responsibility to increase awareness of evidence-based practices that promote the health and well-being of those we serve. When ART is used responsibly, the benefits usually

“However, we must not close our eyes to the well-documented risks and the potential misuse of what is, otherwise, a marvel of modern medicine – the ability to artificially assist nature in the reproduction of our species.”

outweigh the risks, bringing the joy of a new life to many who would otherwise never be able to share that experience. However, we must not close our eyes to the well-documented risks and the potential misuse of what is, otherwise, a marvel of modern medicine – the ability to artificially assist nature in the reproduction of our species.

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Applications for a Mobile Life: In Life, Part 3 of 3 Social and Mobile Media for the Neonatologist

By Clara H. Song, MD

“Social & Mobile Media for the Neonatologist” by Dr. Song, is a periodic column in *Neonatology Today*. Dr. Song created and moderates the social media outlets for the American Academy of Pediatrics, Section on Perinatal Pediatrics, as well as the NICU at the Children’s Hospital at OU Medical Center. She holds workshops and speaks regionally and nationally on the topic of social communication for the healthcare professional, including: the AAP Perinatal Section Spring meeting, yearly, and the 2011 *NEO: The Conference for Neonatology*.

In medicine, we often discuss the ever-popular topic of “Work/Life balance.” As a new mother, I am starting to doubt if “Work” and “Life” can ever really be balanced. One or the other always seems to need more attention on any given day. Life can pass you by, as they say, and doesn’t really like to wait for anyone. So, when the balance leans towards Work, thoughtful and creative apps can help by giving us quick access to useful how-to tips or just fun stuff so that we can get by in Life.

All the following the apps are available at both the iTunes Apple Store and Google Play Store without cost.

FLIPBOARD (flipboard.com): This app is a personalized digital magazine that aggregates articles, photos and videos based on your topic preferences as well as stories from your social media channels. Articles are gathered from sources all over the web, from Time magazine to Twitter, and are displayed on an easy-to-see platform that you can literally “flip” through like a magazine.

CRAFTSY (craftsy.com): Learn arts, crafts and cooking through these classroom style videos. Sewing, gardening, cooking, photography classes can be purchased for online viewing and downloaded for offline viewing later. There are free classes, as well. So, if you’ve always wanted to learn to knit, but never had the time or person to teach you, there’s an app for that now.

KITCHEN STORIES (eng.kitchenstories.de): This app is a cooking class for beginners and expert chefs. It contains how-to videos, easy dishes, complete menus, and kitchen tips/tricks. It is visually appealing and easy to follow.

DAYONE (dayoneapp.com): Day One is a new way to journal from your phone. Journal entries are easily enhanced with photos, location status, and weather updates. Your daily thoughts and experiences can be caught in a flash, literally. Sharing to other social sites and syncing to DropBox or iCloud are also built-in options.

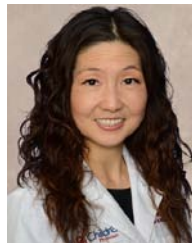
LIFECAKE (lifecake.com): This app is a photo/video journal to chronicle your little one’s life moments in an invite-only venue.

“...when the balance leans towards Work, thoughtful and creative apps can help by giving us quick access to useful how-to tips or just fun stuff so that we can get by in Life.”

Your private Lifecake family view and comment on photos that flow into the app are automatically organized by date and age. You are allowed 10GB of data for free, and unlimited content storage for a fee. There are options to create photo books or even download all your content at once if you ever decide to stop using the app.

FLIPAGRAM (flipagram.com): If you loved playing with your View-Master, then you will have fun with Flipagram. This app allows you to set photos and videos in rapid sequence and play them with music. You end up with short picture/video “grams” that you can pack with memories and send off to Grandma.

NT



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The National Perinatal Association Facilitates Collaboration to Improve Perinatal Care

By Raylene M. Phillips, MD

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



The National Perinatal Association's (NPA) mission is to provide a forum for all healthcare providers and those involved in the care of babies, mothers and families to communicate and work together for the purpose of providing more effective support during the perinatal period. In order to accomplish this mission, we Convene, Educate, Advocate and Integrate. The focus of this column is on what NPA does to "Integrate."

Rather than replicating the work of other organizations and individuals, the NPA facilitates the collaboration of all disciplines as we work together to improve perinatal care. This was demonstrated in the collaborative project that resulted in the Multidisciplinary Guidelines for the Care of Late Preterm Infants, which involved representatives from 20 different organizations who shared their expertise about late preterm infants in an effort to create more uniformity in the management of care for this vulnerable population of newborns. The guidelines were published as a supplement to the *Journal of Perinatology* (2013) 33, S3-S22 (and can be found on the NPA website at www.nationalperinatal.org).

A more recent project facilitated by the NPA integrates the expertise and experience of physicians, nurses, psychologists, social workers, case managers, therapists and parents in the Neonatal Intensive Care Unit (NICU) to develop interdisciplinary recommendations for

program standards to provide psychosocial support for NICU parents, a support system that is entirely missing in most NICUs and highly variable in others. The recommendations are in the final stages of preparation for publication as a supplement to the *Journal of Perinatology* this fall.

The integration of ideas and viewpoints focused on a common concern will be demonstrated in Nashville, TN on October 2-3, 2015 during the symposium entitled *Pregnant Women, Drug Use, and NAS: Experts Share Science & Strategies That Help Women, Babies, and Families*. This symposium is co-sponsored by the National Perinatal Association and National Advocates for Pregnant Women in a partnership that supports our common interest in improving the care provided for women and families in the perinatal period. The symposium will include experts who represent diverse perspectives including obstetric and neonatal medicine, nursing, psychology, so-

“A more recent project facilitated by the NPA integrates the expertise and experience of physicians, nurses, psychologists, social workers, case managers, therapists and parents in the Neonatal Intensive Care Unit to develop interdisciplinary recommendations for program standards to provide psychosocial support for NICU parents, a support system that is entirely missing in most NICUs and highly variable in others.”

cial services, the judicial system, drug rehabilitation, and the women and families involved. To register: www.nationalperinatal.org/event-1993544.

Drug use during pregnancy is a problem that has been around for a long time but is growing exponentially in the United States and the world. Optimal management before and during pregnancy and the complex issues that arise for women and their babies after birth are fraught with myths and facts, preconceived ideas and reality. Only by integrating multiple perspectives can we catch a glimpse of a “whole” picture and work together towards effective interventions and support systems to benefit all those involved.

Please join us in Nashville for a meeting that will provide cutting-edge science and practical strategies we need to help women, babies and families affected by drugs during pregnancy.

We also invite you to join NPA and share in our efforts to better support mothers, babies and families. For more information, see the NPA website at www.nationalperinatal.org.

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Medical News, Products & Information

Compiled and Reviewed by Tony Carlson, Senior Editor

Choosing Wisely® In Newborn Medicine: Five Opportunities To Improve Health Outcomes and Reduce Costs

Newswise - Advances in technology have spurred better outcomes for infants treated in Neonatal Intensive Care Units (NICU), but parents and physicians need to work together to avoid unnecessary and potentially harmful tests and treatments, according to new Choosing Wisely® recommendations developed by neonatologists at Beth Israel Deaconess Medical Center (BIDMC) and published online in *Pediatrics*, the scientific journal of the American Academy of Pediatrics (AAP).

“Infant mortality has dropped dramatically over the past 50 years, with almost all of the impact resulting from care to the mother prior to a high-risk birth or to intensive care provided to the baby afterward,” said DeWayne Pursley, MD, MPH, FAAP, Chair of the Department of Neonatology and Pediatrician-in-Chief at BIDMC and senior author of the recommendations published in the August issue of *Pediatrics*.

“Advanced tests and treatments have been important factors in that drop, but we need to use them more wisely.”

Pursley said the recommendations are based on the premise there are a number of low-value tests and treatments used in newborn care around the country: “Eliminating routine use of these tests and treatments and focusing only on cases where they are justified could both increase care quality and reduce unnecessary costs.”

To that end, Pursley and his colleagues set out to identify opportunities to improve care of newborns through AAP’s newest list of recommendations in the Choosing Wisely® campaign, an initiative of the ABIM Foundation. The Top 5 recommendations focus on the routine use of antibiotics and anti-reflux medications as well as unnecessary x-rays, MRIs and overnight lung activity monitoring.

“There is insufficient evidence that these tests and treatments lead to healthier babies,” said Pursley, adding that overuse of certain medications and treatments could, in fact, be harmful to infants.

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The AAP Section on Perinatal Pediatrics conducted a national survey of pediatricians, neonatologists and pediatric medical and surgical specialists who were asked to consider a range of tests and treatments conducted on high- and low-risk newborns. Respondents provided examples that, in their opinion, lacked evidence of effectiveness, were associated with evidence of ineffectiveness, or unnecessarily used staff or material resources. More than 1,000 respondents offered 2,870 suggestions. An expert panel led by Pursley reviewed and analyzed the responses to identify the Top 5:

1. Avoid routine use of anti-reflux medications for treatment of symptomatic gastroesophageal reflux disease (GERD) or for treatment of apnea and desaturation in preterm infants.
2. Gastroesophageal reflux is normal in infants, but there is minimal evidence that reflux causes interruptions in breathing (apnea) and low blood oxygen concentration (desaturation). In fact, several studies show that the use of some anti-reflux medications may have adverse physiologic effects, including bowel tissue death, infection, hemorrhage or patient death.
3. Avoid use of antibiotics for longer than 48 hours in the absence of bacterial infection.
4. There is not enough evidence to support antibiotic treatment for more than 48 hours to rule out bacterial infection in preterm infants who do not show symptoms. Prolonged antibiotic use may be associated with bowel tissue death and patient death in extremely low-birth weight infants.
5. Avoid routine use of pneumograms for pre-discharge assessment of ongoing and/or prolonged apnea of prematurity.

Cardio-respiratory events are common in both term and pre-term infants. Pneumograms – recordings of breathing effort, heart rate, oxygen level and air flow from the lungs during sleep – are often prescribed as part of pre-discharge assessments of ongoing or prolonged sleep apnea of premature babies. Although there may be a role for pneumograms in cases in which the cause of such events is in doubt, the authors note that their routine use to monitor respiratory function have not been shown to reduce acute, life-threatening events or mortality.

- Avoid routine daily chest radiographs without an indication for intubated infants.
- The authors note that intermittent chest x-rays may identify unexpected findings, but “there is no evidence documenting the effectiveness of daily chest x-rays in reducing adverse outcomes for intubated infants. Further, this practice is associated with increased radiation exposure.”

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- No abstract should be submitted.
- The main text of the article should be written in informal style using correct English. The final manuscript may be between 400-4,000 words, and contain pictures, graphs, charts and tables. Accepted manuscripts will be published within 1-3 months of receipt. Abbreviations which are commonplace in pediatric cardiology or in the lay literature may be used.
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- Avoid routine screening term-equivalent or discharge brain MRIs in pre-term infants.

and Jeffrey D. Horbar, MD, of the University of Vermont and the Vermont Oxford Network (VON) in Burlington, VT.

The authors advise against the routine use of brain magnetic resonance imaging (MRI) in pre-term infants to identify signs of potential long-term neurodevelopmental issues. Pursley notes that normal MRI brain scans of high-risk babies suggest a low-risk of neurodevelopmental problems. However, an abnormal scan only suggests a risk of problems in 50% of high-risk babies. Significantly, the recommendations for the continued testing of these infants rarely change as a result of the study, and some parents simply choose not to have their babies tested when the results may not offer a definitive prognosis.

Ho was supported by the Agency for Healthcare Research and Quality National Research Service Award institutional training grant (5T32HS0000631-21). Horbar is chief executive officer of VON. Ho, Dukhovny, Zupancic, Goldmann and Pursley have received honoraria from VON.

Beth Israel Deaconess Medical Center is a patient care, teaching and research affiliate of Harvard Medical School and consistently ranks as a national leader among independent hospitals in National Institutes of Health funding.

“There is a fair amount of variation in neonatal clinical practice around the country,” Pursley said. “This Top 5 list focuses on five specific opportunities to provide better, higher-value neonatal care, but other low-value tests and treatments are used routinely. We hope that hospitals and newborn care providers will use this list as a starting point in efforts to improve care quality and avoid unnecessary tests and treatments.”

BIDMC is in the community with Beth Israel Deaconess Hospital-Milton, Beth Israel Deaconess Hospital-Needham, Beth Israel Deaconess Hospital-Plymouth, Anna Jaques Hospital, Cambridge Health Alliance, Lawrence General Hospital, Signature Healthcare, Beth Israel Deaconess HealthCare, Community Care Alliance and Atrius Health. BIDMC is also clinically affiliated with the Joslin Diabetes Center and Hebrew Rehabilitation Center and is a research partner of Dana-Farber/Harvard Cancer Center and The Jackson Laboratory. BIDMC is the official hospital of the Boston Red Sox. For more information, visit www.bidmc.org.

“In general, newborn care providers do a good job communicating with families about the care of their babies, but there is always room to do better,” added first author Timmy Ho, MD, FAAP, a neonatologist at BIDMC. Our hope is that caregivers and families will use this list as a starting point in discussions about tests and treatments and whether or not they add value to a baby’s care.”

Seizures in Neonates Undergoing Cardiac Surgery Underappreciated and Dangerous According to Report in The Journal of Thoracic and Cardiovascular Surgery

In addition to Pursley and Ho, who are also affiliated with Boston Children’s Hospital (BCH) and Harvard Medical School (HMS), co-authors include: Dmitry Dukhovny, MD, of BIDMC; John AF Zupancic, MD, ScD of BIDMC, BCH and HMS; Don A. Goldmann, MD, of BCH, the Institute for Healthcare Improvement in Cambridge, MA and HMS;

Newswise – Summary: In 2011, the American Clinical Neurophysiology Society issued a guideline recommending that neonates undergoing cardiac surgery for repair of congenital heart disease be placed on continuous electroencephalographic (EEG) monitoring



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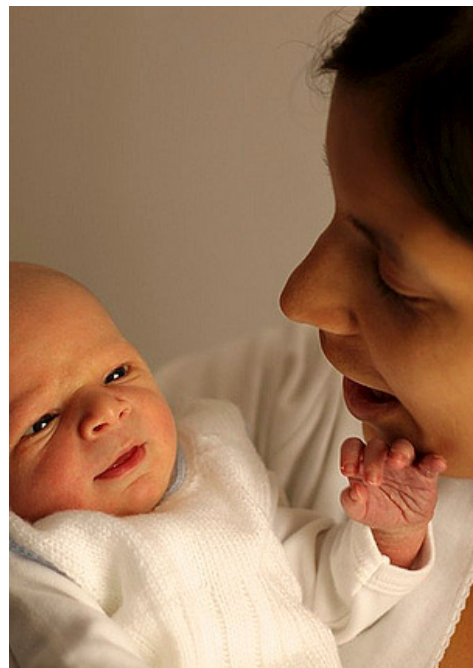
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after surgery to detect seizures. These recommendations followed reports that seizures are common in this population, may not be detected clinically, and are associated with adverse neurocognitive outcomes. Yet, in a discussion at the 2014 Annual Meeting of The American Association for Thoracic Surgery, 80% to 90% of the audience was not following these recommendations. In this report from The Children's Hospital of Philadelphia, investigators present the results of implementing these recommendations. They found that seizures were not uncommon, would not have been detected without EEG monitoring, and that neonates who had seizures faced a significantly higher risk of death.

With mounting concerns about postoperative seizures, doctors at The Children's Hospital of Philadelphia placed 161 neonates who had undergone cardiac surgery on continuous EEG monitoring. They found that 8% of the neonates experienced EEG seizures and 85% of these were unrecognized clinically. Many of the seizures were severe, and the seizure group faced a higher risk of death, according to a report in *The Journal of Thoracic and Cardiovascular Surgery*, the official publication of the American Association for Thoracic Surgery (AATS).

"In their article, Naim and colleagues have clearly pointed out that if we don't carefully assess for seizure activity with EEG monitoring, we will not identify these at-risk neonates," stated Carl L. Backer, MD, Division of Cardiovascular-Thoracic Surgery, and Bradley S. Marino, MD, MPP, MSCE, Division of Cardiology, both at the Ann & Robert H. Lurie Children's Hospital of Chicago, in an accompanying editorial. "It is clearly no longer adequate for investigators reporting outcomes after neonatal cardiac surgery to state that neonates did not have postoperative neurologic complications if they

do not use continuous EEG monitoring."

Conducting a quality improvement project, the team at The Children's Hospital of Philadelphia implemented continuous EEG monitoring in neonates (≥ 30 days corrected gestational age) following cardiac surgery for repair of Congenital Heart Disease. During an 18-month period from June 15, 2012 to December 31, 2013, records of continuous EEG (CEEG) were obtained from 94% (161) of 172 surgeries.

CEEG began within six hours of the patient returning to the cardiac intensive care unit after surgery. Monitoring continued for 48 hours if no seizures were detected and for 24 hours after the last seizure if a seizure occurred. EEG technologists were present for EEG monitoring and interpretation at all times.

The neonates had a range of cardiac defects, with 42% Class I (two ventricles with no aortic arch obstruction), 22% Class II (two ventricles with aortic arch obstruction), 9% Class III (single ventricle with no aortic arch obstruction), and 27% Class IV (single ventricle with aortic arch obstruction). A variety of repairs were performed, including Stage I Norwood (27%) and arterial switch operations (16%).

Bedside clinicians identified events such as abnormal body movements, hypertension, or tachycardia in 32 neonates – but none of these events had associated abnormal EEG activity. However, 13 of the 161 neonates (8%) had EEG seizures. Of these, 85% (11) were not detected clinically. "This indicates that bedside clinical assessment for seizures without CEEG is unreliable," explained lead investigator Maryam Y. Naim, MD, Division of Cardiac Critical Care, Departments of Anesthesiology and Critical Care Medicine and Pediatrics, The Children's Hospital of Philadelphia, and As-



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Adults who had been born very prematurely and/or extremely underweight scored significantly higher on all but two of the personality traits--conscientiousness and openness--than their peers born at term.

Taking account of potentially influential risk factors did not alter the magnitude of these differences.

Adults who had been born very prematurely and/or extremely underweight also reported significantly higher levels of autistic spectrum behaviours, introversion, neuroticism, agreeableness and lower levels of risk-taking.

The personality traits that best described the profile of adults who had been born very prematurely and/or extremely underweight were: introversion, risk aversion, autistic spectrum behaviours and neuroticism. The findings held true even after taking lower intelligence into account.

This cluster of traits describes a 'socially withdrawn personality,' or someone who is easily worried, less socially engaged, less interested in risk taking, and less communicative, say the researchers.

"The higher scores of [very premature/low birthweight] adults on the socially withdrawn scale are most likely to be the result of alterations in their brain structure and functioning due to the amalgam of changes in brain development related to premature birth and prenatal and neonatal insult," write the researchers.

They go on to suggest that these children are likely to be exposed to considerable stressors in neonatal intensive care, which may affect brain development and adult adaptation, added to which early birth may prompt parents to be over-protective.

The physiological circumstances of these babies' birth might help explain the higher rates of career and relationship difficulties in adulthood, say the researchers.

The evidence shows that many adults born very premature/low birthweight are less likely to go on to higher education or get well paid jobs; and they find it harder to make friends, find long term partners, and become a parent, the researchers point out.

Admission Rates Increasing for Newborns of All Weights in NICUs

Admission rates are increasing for newborns of all weights at Neonatal Intensive Care Units (NICUs) in the United States, raising questions about possible overuse of this highly specialized and expensive care in some newborns, according to an article published online by *JAMA Pediatrics*.

The neonatal mortality rate has fallen more than four-fold (from 18.73 per 1,000 live births to 4.04 per 1,000 live births in 2012) since the first NICU opened in the United States 55 years ago

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to provide highly specialized care to pre-mature and sick infants.

Few studies have looked beyond very low-birth-weight infants admitted to the NICU to examine how neonatal care relates more broadly to newborn care. A 2003 revision to the U.S. Standard Certificate of Live Birth includes a new field to indicate whether a newborn was admitted to the NICU, which allows researchers to study trends in neonatal intensive care for the majority of the U.S. newborn population across time.

Wade Harrison, MPH, and David Goodman, MD, MS, of the Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Lebanon, NH, looked at data for nearly 18 million live births to U.S. residents from January 2007 through December 2012 in 38 states and the District of Columbia.

The authors found overall admission rates increased from 64.0 to 77.9 per 1,000 live births and that admission rates increased for all birth-weight categories.

More specifically, the study reports that in 2012 there were 43 NICU admissions per 1,000 normal-birth-weight infants (2,500 to 3,999 grams), while the admission rate for very low-birth weight infants (less than 1,500 grams) was 844.1 per 1,000 live births.

From 2007 to 2012, NICUs increasingly admitted term infants of higher birth weights and by 2012, nearly half of all NICU admissions were for normal-birth-weight infants or for those born at 37 weeks gestation or older, according to the results.

The authors note they cannot say from their data whether the lower admission



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rates in 2007 or the higher rates seen more recently are closer to the correct rate.

"Newborns in the United States are increasingly likely to be admitted to a NICU, and these units are increasingly caring for normal-birth-weight and term infants. The implications of these trends are not clear, but our findings raise questions about how this high-intensity resource is being used," the study concludes.

(JAMA Pediatr. Published online July 27, 2015. doi:10.1001/jamapediatrics.2015.1305.

In a related editorial, Aaron E. Carroll, MD, MS, of the Indiana University School of Medicine, Indianapolis, writes: "Once again, it is critical to stress that the important work of Harrison and Goodman does not prove that the increased NICU admissions we are seeing are fraudulent or even merely wasteful. It is entirely possible that the admissions are justified. However, there is no doubt that they are expensive and carry potential harm. If hospitals want to argue that NICUs are necessary, they will need to prove that the need exists, especially in light of the increasing share of infants admitted who are at or near full term. If hospitals are unable to demonstrate that NICUs are necessary, then it is very likely that, at some point in the near future, policies will force them to reduce those admissions, which will have major implications for NICU and hospital finances."(JAMA Pediatr.

Published online July 27, 2015. doi: 10.1001/jamapediatrics.2015.1597.

Letters to the Editor

Neonatology Today welcomes and encourages Letters to the Editor. If you have comments or topics you would like to address, please send an email to: LTE@Neonate.biz and let us know if you would like your comment published or not.

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News and Information for BC/BE Neonatologists and Perinatologists

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