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Dr. Mozib Newborn Foundation
The Carlo GNS Center for Saving Lives at Birth
Vishwa Mahesh Parivaar
Autism Care Network Foundation

And
GNS Down Syndrome Foundation
Newborn Foundation of Azerbaijan
GNS Bangladesh Newborn Foundation
GNS Foundation of Germany
Global Newborn Society Foundation of Italy
Mongolian Association of Obstetrics Gynecology and Neonatology
Foundation for Human Milk Feeding in the Islamic World
The organization, Protecting Brains and Saving Futures, Brasil
Association of Neonatologists in the United Kingdom
Polish Nursing Association - Płock, Poland
Panlibyan Neonatal Association
Association for Indigenous Peoples in India
Association for Newborn Care in Pakistan
GNS Association for Perinatal Care
Association for Infant Nutrition in the Middle East
Sociedad Latinoamericana de Residentes de Neonatologia (SolaReNeo)
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GNS Forum for Transgenerational Inheritance
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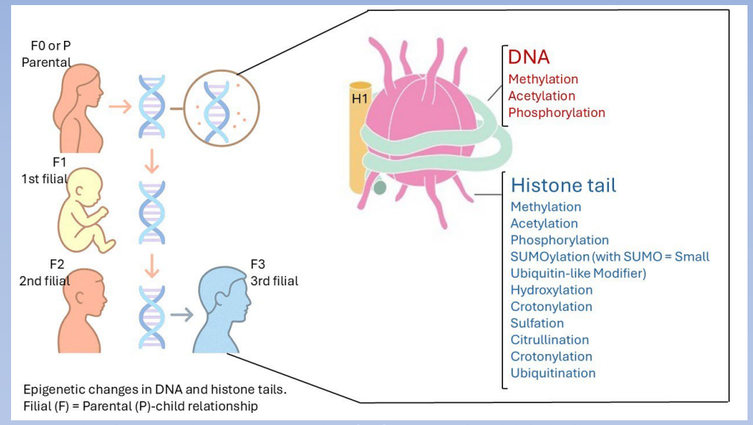
GNS Forum for Data Analytics
GNS Forum for Nanomaterials
Neonatology Branch of the Chilean Pediatric Society
Dudeja GNS Center for Infectious Diarrheal Diseases
Anatolian Midwives Association
GNS Western Australia
Perinatal Society of Singapore
Pioneers - looking for sustainable ways to reduce infant mortality
Bhutan Neonatal Care Forum
Global Newborn Society Iran Chapter
National Federation of Neonatologists of Mexico
College of Neonatologists of the State of Jalisco, Mexico
The Skylar Project
International Society for Marginalized Lives
Friends Aid Africa, Bukedea, Uganda
Society of Bacteriophage Research and Therapy
GNS Center for Computational Scientific Methodology
GNS International Association of Neonatal POCUS
SABREE Enrichment Academy: Empowering Ability
The Caribbean Association for Hematology and Oncology
First Breath of Life
GNS Neonatal Radiology Forum

Highlighted articles:



Transgenerational Epigenetics

Systemized Systemic Sono Screening (S4) Protocol: Initial Findings
Neonatologists' Use of Social Media: A Survey Exploring Professional and Personal Practices

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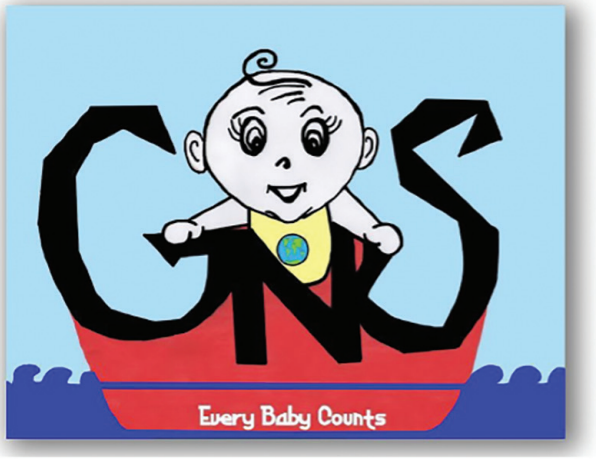

Global Newborn Society

Each time we lose an infant, we lose an entire life and its potential!

Newborn is the official journal of the Global Newborn Society (GNS), a globally active, non-profit organization that is registered as a 501(c)(3) non-profit formation in the United States and is currently being listed as an analogous charity in many other nations. The aim is to enhance research in newborn medicine, understand epidemiology (risk factors) of disease, train healthcare workers, and promote social engagement. The GNS was needed because despite all improvements in medical care, infants remain a high-risk patient population with mortality rates similar to 60-year-olds. We need to remind ourselves that *Every Baby Counts*, and that *Each Time We Lose an Infant, We Lose an Entire Life and its Potential*.

Our logo above, a hand-drawn painting, graphically summarizes our thought-process. There is a lovable little young infant exuding innocent, genuine happiness. The curly hair, shape of the eyes, long eyelashes, and the absence of skin color emphasize that infants need care all over the world, irrespective of ethnicity, race, and gender. On the bib, the yellow background reflects happiness, hope, and spontaneity; the globe symbolizes well-coordinated, worldwide efforts. The age-related vulnerability of an infant, with all the limitations in verbal expression, is seen in being alone in the boat.

The unexpressed loneliness that many infants endure is seen in the rough waters and the surrounding large, featureless sky. However, the shades of blue indicate that the hope of peace and tranquility is not completely lost yet. The acronym letters, GNS, on the starboard are made of cast metal and are pillars of strength. However, the angular rough edges need continued polishing to ascertain adequacy and progress. The red color of the boat symbolizes our affection. The expression "*Every Baby Counts*" seen on the boat's draft below the waterline indicates our commitment to philanthropy, and if needed, to altruism that does not always need to be visible. The shadow behind the picture shows that it has been glued on a solid wall, one built out of our adoption and commitment.

Design of the Journal Cover

The blue color on the journal cover was a careful choice. Blue is the color of flowing water, and symbolizes the abnormalities of blood vascular flow that are seen in many neonatal illnesses. There is a gradual transition in the shades of blue from the top of the cover downwards. The deeper shades of blue on the top emphasize the depth, expertise, and stability, which the renowned authors bring. Light blue is associated with health, healing, tranquility, understanding, and softness, which their studies bring. The small letter "*n*" in the title of the journal, *newborn*, was chosen to emphasize the little size of a newborn baby. The issue editors chose three articles to be specifically highlighted; the two pictures and two titles below reflects an order suggested by them.

Instructions to Authors

The journal welcomes original articles and review articles. We also welcome consensus statements, guidelines, trials methodology, and core outcomes relevant to fetuses/young infants in the first 1000 days. A detailed set of instructions to authors can be seen online at https://www.globalnewbornsociety.org/intructions-for-authors. The manuscripts can be submitted via the online manuscript submission system.

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Breastfeeding: The Natural, Nonpareil, and Nourishing Nexus between a Mother and Her Baby

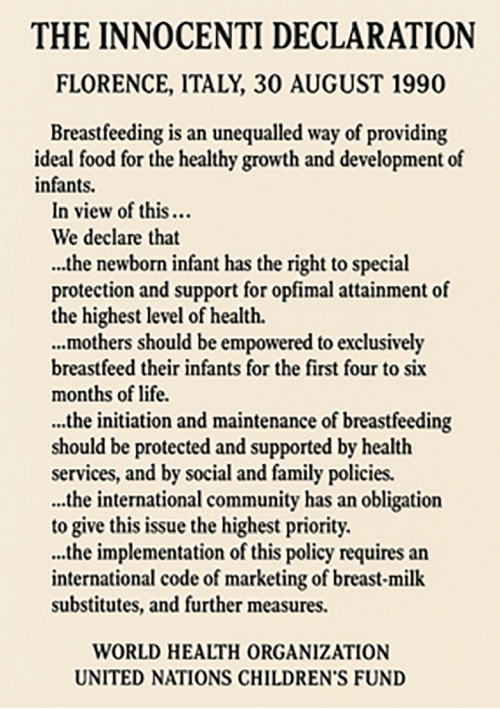
We celebrate the World Breastfeeding Week (WBW) every year from August 1–7 in more than 120 countries.[1] It was launched in 1992 by the World Alliance for Breastfeeding Action[2] in collaboration with the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (renamed as the United Nations Children's Fund in 1953, although the acronym UNICEF was retained).[3] These events followed the 1990 Innocenti Declaration[4] on the protection, promotion, and support of breastfeeding **(Fig. 1)**. This global campaign aims to create awareness, inspire action, and strengthen support for breastfeeding at individual, community, and policy levels.

Breastfeeding is widely recognized as the optimal source of nutrition for infants, providing all essential nutrients required for immediate and long-term infant growth and development.[5–7] Human milk (HM) contains antibodies and immune factors that protect babies from infections such as diarrhea, respiratory illnesses, and ear infections, while also supporting healthy digestion and reducing the risk of allergies, obesity, and chronic diseases later in life.[8,9] The impact of breastfeeding on the cognitive development of the infant and on the emotional bond between the mother and her child is well recognized.[9]

In addition to the benefits to the infant, breastfeeding is equally important for mothers as it promotes postpartum recovery, reduces the risk of breast and ovarian cancers, lowers the likelihood of type 2 diabetes, and enhances the emotional bonding with the baby.[10–12] For the society, it reduces healthcare costs by preventing diseases linked to poor infant feeding practices[12,13] and supports environmental sustainability since breast milk requires no packaging, transport, or waste disposal.[14,15] At the community and national levels, breastfeeding contributes to food security by providing a safe, natural, and renewable food source for infants.[16]

The 1990, the *Innocenti Declaration on the Protection, Promotion, and Support of Breastfeeding* was adopted in Spedale degli Innocenti, a historic children's hospital and orphanage in Florence, Italy.[4,17] It recognized breastfeeding as a unique and irreplaceable way of providing ideal nutrition and protection for infants, while also benefiting mothers and societies.[18] The declaration urged governments and health systems to create supportive environments for breastfeeding and set 4 operational targets: appointing a national breastfeeding coordinator with a multisectoral committee, ensuring that all maternity facilities follow the *Ten Steps to Successful Breastfeeding*,[19] implementing the *International Code of Marketing of Breast-milk Substitutes*,[20,21] and enacting legislation to protect the rights of working women to breastfeed. This landmark declaration laid the foundation for global initiatives such as the Baby-friendly Hospital Initiative[18] and the annual World Breastfeeding Week,[22] and made it a cornerstone document in the development of child health and nutrition policies all over the world.[23]

The WHO and UNICEF recommend early initiation of breastfeeding within the first hour of birth, exclusive breastfeeding for the first 6 months of life,[24] and continued breastfeeding up to two years of age or beyond, along with appropriate complementary feeding.[25–28]



THE INNOCENTI DECLARATION

FLORENCE, ITALY, 30 AUGUST 1990

Breastfeeding is an unequalled way of providing ideal food for the healthy growth and development of infants.

In view of this…

We declare that

…the newborn infant has the right to special protection and support for opfimal attainment of the highest level of health.

…mothers should be empowered to exclusively breastfeed their infants for the first four to six months of life.

…the initiation and maintenance of breastfeeding should be protected and supported by health services, and by social and family policies.

…the international community has an obligation to give this issue the highest priority.

…the implementation of this policy requires an international code of marketing of breast-milk substitutes, and further measures.

WORLD HEALTH ORGANIZATION
UNITED NATIONS CHILDREN'S FUND

Fig. 1: The 1990, the *Innocenti Declaration on the Protection, Promotion, and Support of Breastfeeding* was adopted in Spedale Degli Innocenti, Florence, Italy

Despite these efforts, the rates of exclusive breastfeeding still remain lower than 50% in many regions; we need for advocacy, education, and supportive policies.[29] Each year, the WBW is celebrated with a specific, focused theme such as supporting breastfeeding in the workplace, linking breastfeeding with sustainable development, or strengthening health systems and community networks.[30–32] By engaging governments, healthcare providers, employers, and communities, WBW seeks to emphasize that supporting breastfeeding is a shared responsibility.[3,33]

Moving from this line of discussion, the Global Newborn Society (GNS) continues to grow as a worldwide social movement for improving neonatal care. There has been a recent commitment of a major financial support from the Carlo GNS Center for Saving Lives at Birth (USA) have added momentum. Similarly, the newly established Dr Mozib Newborn Foundation has made major commitments.[34] Since the last issue, two more organizations have adopted the journal. There is a newly formed GNS Neonatal Radiology Forum, and The Caribbean Association for Hematology and Oncology[35] will use the journal for communication of major policy decisions with global fora such as the World Health Organization. The organization, First Breaths of Life, has registered itself with the modified name, First Breath of Life. Currently, our group is comprised of the GNS and 51 other organizations. We consult each other and share scientific data, viewpoints, and our experiences relevant for care of newborn infants in various parts of the world.

In each issue of this journal, our editorial team highlights the achievements of one of our partnering members. Here, we present the efforts of the Pediatrics/Neonatology team at the North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences is a medical institution in India in Shillong, Meghalaya, India **(Fig. 2)**.[36,37] The financial costs of care are largely covered by the Central and State Governments. The medical, nursing, and allied staff attends about 1200 high-risk deliveries from geographically remote areas in the Northeastern part of India.[38] About half need cesarean sections. Twenty percent are premature, and there is a high incidence of small-for-gestation infants. About a fourth need intensive care, with leading diagnoses of prematurity, birth asphyxia, and congenital anomalies (neural tube defects, cleft lip/palate, and heart defects).[38] Northeastern India is a difficult geographical terrain and the provision of healthcare services has had major challenges.[39] The leadership is widely recognized for developing the facility and it now provides a full-range of services.

This journal aims to cover fetal/neonatal problems that begin during pregnancy, at the time of birth, or during the first 1,000 days after birth.[40] As in our previous issues, we present 8 articles here **(Fig. 3)**. Consistent with the aforementioned focus on materanal-infant bonding, we present an important worldwide survey on Kangaroo care (KC).[41] KC is well-recognized as a low cost, effective intervention offering many benefits to the infant, parents, health system and the society;[42–44] there is information on the knowledge, attitudes and practices (KAP) at institutional/regional levels but there are gaps on a global scale.[45,46] In this study, the authors studied KC with 134 clinicians from 32 countries. The awareness and acceptance of KC are generally high among caregivers and parents but disparities exist based on country income levels. There is still a need for more structured training and consistent guidelines to promote equitable and effective kangaroo care practices globally.

There has been an ongoing debate about the ethics of resuscitation of periviable infants all over the world.[47,48] Motijama et al.[49] compared the clinical practices in their neonatal unit in Japan vs. another unit in Australia. They found that routine provision of care to periviable infants born at 22–23 weeks' gestation in Japan[50,51] may have improved the outcomes of those born at 24–27 weeks' gestation. The outcomes in Japan were better, seen as lower frequencies of chronic lung disease, necrotizing enterocolitis, early onset sepsis, severe interventricular hemorrhage, periventricular leukomalacia, retinopathy of prematurity, and mortality. These findings need to be seriously considered in terms of ethics, quality of care, impact on families, and clinical outcomes.[52–63]

Figs. 2A to C: The North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences (NEIGRIHMS) hospital is a major medical center in Northeastern India. It is located in the (A) city of Shillong, in the state of Meghalaya (marked by red dot on the map). (Bi–iii) This region has a forest canopy cover higher than 75% and so the development of physical access with roads and residential facilities was a critical first step; (Ci–ii) With allocation of financial and human resources by the National and State Governments, the infrastructure and livability gradually improved. The NEIGRIHMS hospital was then constructed; (Di–ii) the hospital facility has gradually grown as a major regional medical hub over the last decade and has begun attracting highly qualified professional expertise. Its neonatal intensive care unit now receives complex cases from the entire northeastern region.

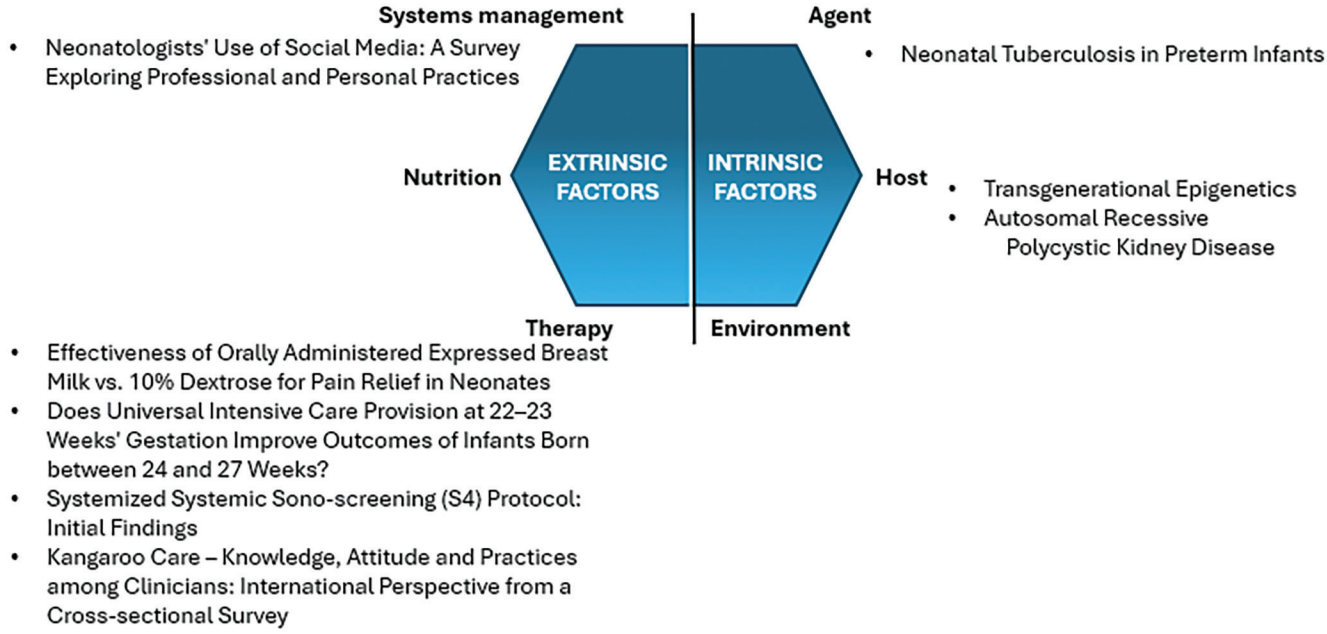


Fig. 3: Areas of focus in the *newborn,* Volume 4, Issue 3. We have expanded the traditional agent-host-environment trinodal disease model to a hexagonal system. The three additional foci represent extrinsic factors that can affect health—those originating in therapy, nutrition, and systems management are shown. This issue covers 4 nodes, with articles focused on an agent, host factors, therapy/monitoring systems, and systems management.

Krizam et al.[64] have described three premature infants with congenital tuberculosis. The first was born to a mother with tuberculosis at 27 weeks' gestation. The infant tested negative in her initial screening for tuberculosis. However, she deteriorated on postnatal day 40 and the gastric aspirates showed acid-fast bacilli. Their other patients were a pair of dichorionic-diamniotic twins born at 26^{+5} weeks gestation. They also had a delayed-onset respiratory illness at 5–7 weeks after birth. Congenital tuberculosis can present after a variable number of days/weeks after birth and needs to be considered in the differential diagnosis of infants who show clinical deterioration despite conventional antibiotics.[65,66]

Pain management is often overlooked in neonates undergoing minor procedures. Rajkumar et al.[67] have compared the analgesic effects of oral 10% dextrose vs. expressed breast milk (EBM) in neonates before they received their first dose of hepatitis B vaccination. They conducted a single-center prospective observational study; each infant received either 2 mL of EBM or 10% dextrose 2 minutes before vaccination and measured pain (Neonatal Infant Pain Scale[68]), duration of cry, and heart rate. Oral 10% dextrose was more effective in reducing procedural pain. This is an important study for two reasons: (a) In neonates, pain is not only an unpleasant sensory/emotional experience but it might even cause neural tissue damage.[69] Sweet-tasting solutions such as sucrose and concentrated dextrose can prevent pain in neonates by stimulating the release of endogenous opioids and activating μ receptors;[70] and (b) even though their findings were similar to those previously reported with 25% dextrose,[71] oral 10% dextrose may be safer as it might not change plasma glucose levels to the same extent.[72] It was also more convenient because their neonatal unit stored 10%, but not 25%, dextrose at the bedside.

Singh and Maheshwari[73] have presented a review of transgenerational epigenetic inheritance, where the epigenetic markers can be transmitted from one generation to at least two subsequent generations of offspring without altering the primary structure of DNA. Epigenetic marks include DNA methylation, several histone modifications, noncoding RNAs, and chromatin structural changes.[74,75] Rodent studies show transgenerational effects of endocrine disruptors, pesticides, and nutritional deficiencies, linking ancestral exposures to altered metabolism, fertility, and disease risk in unexposed descendants.[76,77] Transgenerational epigenetics represents a rapidly evolving field that challenges traditional views of inheritance by suggesting that environmentally induced epigenetic information can persist beyond direct exposure and influence phenotypes across generations.[78] There is a need for human mass studies covering several generations.[79] Newer computational models for deductive/inductive projections from numerically limited cohorts may help in making robust predictions and generalizations.[80]

Several teams within the GNS are actively exploring whether a Systematized Systemic Sono-screening (S4) evaluation,[81] performed as an extension of a physical examination in all infants to predict/identify problems before these become clinically evident, could be useful. This approach draws inspiration from our obstetrician colleagues, who have successfully and effectively performed serial maternal-fetal evaluations during pregnancy. These S4 evaluations differ from the earlier point-of-care ultrasound (POCUS), where a focused sonographic evaluation is performed to assess/monitor critically ill patients.[82] S4 evaluations are being visualized as a 13-point screen: *cranial* (1) severe intraventricular hemorrhage (grades 3–4); *cardiovascular*: (2) position of central line(s), (3) preload in inferior vena cava and right atrium, (4) left ventricular ejection fraction, (5) patency of the ductus arteriosus, (6) coarctation of the aorta; *lungs*: (7) lung parenchyma and (8) pleural effusion – with its high specificity for pneumonia; *abdomen*: (9) liver size and ascites, (10) kidney and

bladder size; (11) *vertebral column*, particularly at the thoracolumbar verbral junction; (12) *genitalia*; and (13) *hip joints*. This manuscript reports a pictorial essay from a recent screening of past medical records.[81] The authors noted a high incidence of intracardiac thrombi in the right cardiac chambers. Such thrombi have been described earlier, and have been associated with the longer durations for which umbilical venous catheters (UVCs) were used[83] or lower blood flow velocities in the right heart chambers.[84] However, not every patient in this cohort had received a UVC. We may still need further investigation of risk factors; hemodynamic measurements can vary at specific location(s) at various time-points in the cardiac cycle and with altered vascular resistance/ventricular hypertrophy.[85] Alternative factors such as inherited thrombophilic abnormalities may also need investigation.[86]

Vereen et al.[87] have discussed the use of social media[88-90] by neonatologists for professional purposes. An anonymous online survey from the American Academy of Pediatrics was answered by 223 neonatologists. Most reported that they "Never" or "Rarely" contribute, seek or scan social media for medical knowledge. Opinions on the impact of social media on clinical practice were mixed; younger professionals viewed these platforms more positively. Neonatologists might not be using social media at the same rate as families which could contribute to communication gaps as families increasingly use social media for information and support. Further research is needed to assess the effects of social media on healthcare quality and resource allocation and to develop strategies to mitigate misinformation.

Finally, we present illustrative images suggestive of autosomal recessive polycystic kidney disease[91–93] from a young child born at full-term gestational age. She had a prior history of repeated episodes of fevers, and during her systemic evaluation, was noted to have abnormal plasma renal function indices. Renal ultrasound showed enlarged kidneys with increased echogenicity, multiple cysts of varying sizes, and loss of normal corticomedullary differentiation. Sonographic images of the liver showed two anechoic cystic areas, representing possibly a combination of von-Meyenburg complexes[94] (biliary hamartomas) and focal intrahepatic biliary dilation indicating Caroli disease.[95]

References

1. WHO. World Breastfeeding Week 2025 Geneva, Switzerland: World Health Organization; 2025 [cited 2025]. Available from: https://www.who.int/campaigns/world-breastfeeding-week/2025.
2. WABA. World Alliance for Breastfeeding Action Penang, Malaysia: World Alliance for Breastfeeding Action (WABA); 2025 [cited 2025]. Available from: https://waba.org.my/.
3. Sande A. Why we all need to work together to prioritize breastfeeding. China CDC Wkly. 2025 ;7(31):1011–1013. PMID: 40831614. doi: 10.46234/ccdcw2025.171.
4. WABA. 1990-Innocenti-Declaration Penang, Malaysia: World Alliance for Breastfeeding Action; 1990. Available from: https://worldbreastfeedingweek.org/2018/wp-content/uploads/2018/07/1990-Innocenti-Declaration.pdf.
5. Donda K, Maheshwari A. Human milk lipids induce important metabolic and epigenetic changes in neonates. Clin Perinatol. 2022;49(2):331–353. PMID: 35659090. doi: 10.1016/j.clp.2022.02.006.
6. Maheshwari A, Mantry H, Bagga N, Frydrysiak-Brzozowska A, Badarch J, Rahman MM. Milk fat globules: 2024 Updates. Newborn (Clarksville). 2024;3(1):19–37. PMID: 39474586. doi: 10.5005/jp-journals-11002-0085.
7. Maheshwari A. Fats in human milk: 2022 Updates on Chemical Composition. Newborn (Clarksville, Md). 2022;1(4):384–396. doi: 10.5005/jp-journals-11002-0050.
8. Morniroli D, Consales A, Crippa BL, Vizzari G, Ceroni F, Cerasani J, et al. The antiviral properties of human milk: A multitude of defence tools from mother nature. Nutrients. 2021;13(2). PMID: 33671491. doi: 10.3390/nu13020694.
9. Bagga N, Lui K, Liubšys A, Rahman MM, Singh S, Mynak ML, et al. Human milk. In: Maheshwari A, editor. Principles of Neonatology. Philadelphia, Pennsylvania, USA: Elsevier; 2024. pp. 112–119.
10. Dieterich CM, Felice JP, O'Sullivan E, Rasmussen KM. Breastfeeding and health outcomes for the mother-infant dyad. Pediatr Clin North Am. 2013;60(1):31–48. PMID: 23178059. doi: 10.1016/j.pcl.2012.09.010.
11. Purkiewicz A, Regin KJ, Mumtaz W, Pietrzak-Fiecko R. Breastfeeding: The multifaceted impact on child development and maternal well-being. Nutrients. 2025;17(8). PMID: 40284191. doi: 10.3390/nu17081326.
12. Patnode CD, Henrikson NB, Webber EM, Blasi PR, Senger CA, Guirguis-Blake JM. Breastfeeding and health outcomes for infants and children: A systematic review. Pediatrics. 2025;156(1). PMID: 40240318. doi: 10.1542/peds.2025-071516.
13. Quesada JA, Mendez I, Martin-Gil R. The economic benefits of increasing breastfeeding rates in Spain. Int Breastfeed J. 2020;15(1):34. PMID: 32366305. doi: 10.1186/s13006-020-00277-w.
14. Mohapatra I, Samantaray SR. Breastfeeding and environmental consciousness: A narrative review of environmental implications and potential contributions to reduce waste and energy consumption. Cureus. 2023;15(9):e45878. PMID: 37885540. doi: 10.7759/cureus.45878.
15. Becker G, Ryan-Fogarty Y. Reliance on pumped mother's milk has an environmental impact. Children (Basel). 2016;3(3). PMID: 27626456. doi: 10.3390/children3030014.
16. Guerrero CH, Cremades R, Sierra-Diaz E, Lopez Flores ML, Murcia-Baquero LM, Sandoval-Pinto E. Association of food security with breastfeeding practices: A scoping review. Cureus. 2024;16(5):e61177. PMID: 38933626. doi: 10.7759/cureus.61177.
17. Summers B. Spedale Degli Innocenti, the Foundling Hospital in Florence, Italy. Med Humanit. 2016;42(2):141–142. PMID: 26612547. doi: 10.1136/medhum-2015-010774.
18. Pound CM, Unger SL, Canadian Paediatric Society HPSN, Gastroenterology C. The Baby-friendly Initiative: Protecting, promoting and supporting breastfeeding. Paediatr Child Health. 2012 ;17(6):317–327. PMID: 23730170.
19. Saadeh R, Akre J. Ten steps to successful breastfeeding: a summary of the rationale and scientific evidence. Birth. 1996;23(3):154–160. PMID: 8924101. doi: 10.1111/j.1523-536x.1996.tb00476.x.
20. Lutter CK. The international code of marketing of breast-milk substitutes: lessons learned and implications for the regulation of marketing of foods and beverages to children. Public Health Nutr. 2013;16(10):1879–1884. PMID: 23034164. doi: 10.1017/S1368980012004235.

21. Both D. The international code of marketing of breastmilk substitutes : History, content, and significance. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2018;61(8):1008–1011. PMID: 29947854. doi: 10.1007/s00103-018-2765-4.
22. Olafuyi O, Pansari A, Anderson PO, Allegaert K. Editorial: World breastfeeding week 2024: an obstetric and pediatric pharmacology perspective. Front Pharmacol. 2025;16:1671327. PMID: 40894215. doi: 10.3389/fphar.2025.1671327.
23. Sobti J, Mathur GP, Gupta A, Who. WHO's proposed global strategy for infant and young child feeding: a viewpoint. J Indian Med Assoc. 2002;100(8):502–504, 506. PMID: 12675182.
24. WHO. Exclusive breastfeeding for six months best for babies everywhere Geneva, Switzerland: World Health Organization; 2011 [Available from: https://www.who.int/news/item/15-01-2011-exclusive-breastfeeding-for-six-months-best-for-babies-everywhere].
25. WHO/UNICEF. Global strategy on infant and young child feeding Geneva, Switzerland: World Health Organization; 2003. Available from: https://www.who.int/nutrition/publications/infantfeeding/9241562218/en/.
26. Davis/USAID/FANTA WUIU. Indicators for assessing infant and young child feeding practices. Part 3: country profiles Geneva, Switzerland: World Health Organization; 2008. Available from: http://www.who.int/nutrition/publications/infantfeeding/9789241599757/en/.
27. Neves PAR, Vaz JS, Maia FS, Baker P, Gatica-Dominguez G, Piwoz E, et al. Rates and time trends in the consumption of breastmilk, formula, and animal milk by children younger than 2 years from 2000 to 2019: analysis of 113 countries. Lancet Child Adolesc Health. 2021;5(9):619–630. PMID: 34245677. doi: 10.1016/S2352-4642(21)00163-2.
28. Neovita-Study-Group. Timing of initiation, patterns of breastfeeding, and infant survival: prospective analysis of pooled data from three randomised trials. Lancet Glob Health. 2016 ;4(4):e266–275. PMID: 27013313. doi: 10.1016/S2214-109X(16)00040-1.
29. Reddy NS, Dharmaraj A, Jacob J, Sindhu KN. Exclusive breastfeeding practices and its determinants in Indian infants: findings from the National Family Health Surveys-4 and 5. Int Breastfeed J. 2023;18(1):69. PMID: 38124065. doi: 10.1186/s13006-023-00602-z.
30. Ramesh N, Siddaiah A, Joseph B. Promoting workplace breastfeeding practices. Indian J Occup Environ Med. 2023;27(4):275–277. PMID: 38390490. doi: 10.4103/ijoem.ijoem_309_23.
31. ILO. Maternity at work: A review of national legislation findings from the ILO database of conditions of work and employment laws Geneva, Switzerland: International Labor Organization; 2010. Available from: https://www.ilo.org/wcmsp5/groups/public/---dgreports/---dcomm/---publ/documents/publication/wcms_124442.pdf.
32. Naylor AJ. Baby-friendly hospital initiative. Protecting, promoting, and supporting breastfeeding in the twenty-first century. Pediatr Clin North Am. 2001;48(2):475–483. PMID: 11339166. doi: 10.1016/s0031-3955(08)70039-7.
33. Abdulwadud OA, Snow ME. Interventions in the workplace to support breastfeeding for women in employment. Cochrane Database Syst Rev. 2012;10(10):CD006177. PMID: 23076920. doi: 10.1002/14651858.CD006177.pub3.
34. Rahman MM. Dr. Mozib Newborn Foundation Dhaka, Bangladesh: Dr. Mozib Newborn Foundation; 2025;4(3). Available from: https://drmnf.org/.
35. CAOH. The Caribbean Association for Oncology and Hematology (CAOH) Cocorite, Trinidad & Tobago: The Caribbean Association for Oncology and Hematology; 2017 [cited 2025. Available from: https://caohcaribbean.org/?v=accc9105df53].
36. NEIGRIHMS. NEIGRIHMS Shillong, India: North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences; 2025. Available from: https://neigrihms.gov.in/pediatric.html#intro.
37. Khongwar D, Hajong R, Saikia J, Topno N, Baruah AJ, Komut O. Clinical study of burn patients requiring admission: A single center experience at North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences. J Family Med Prim Care. 2016;5(2):444–448. PMID: 27843858. doi: 10.4103/2249-4863.192337.
38. Bhatt DC, Neog R. Health and development concerns of the north-east. Health Millions. 1997 ;23(3):3. PMID: 12292997.
39. Aggarwal S, Simmy S, Mahajan N, Nigam K. Challenges experienced by health care workers during service delivery in the geographically challenging terrains of North-East India: Study involving a thematic analysis. JMIR Form Res. 2024;8:e57384. PMID: 39255009. doi: 10.2196/57384.
40. Global-Newborn-Society. Newborn Clarksville, MD, USA: Global Newborn Society; 2021 [updated 2024. Available from: https://www.globalnewbornsociety.org/our-scientific-journal-newborn].
41. Jani P, Maheshwari A. Kangaroo care – Knowledge, Attitudes, and Practices among Clinicians: International Perspective from a Cross-Sectional Survey. Newborn (Clarksville, Md). 2025;4(3):115–121. doi: 10.5005/jp-journals-11002-0136.
42. Campbell-Yeo ML, Disher TC, Benoit BL, Johnston CC. Understanding kangaroo care and its benefits to preterm infants. Pediatric Health Med Ther. 2015;6:15–32. PMID: 29388613. doi: 10.2147/PHMT.S51869.
43. Widstrom AM, Lilja G, Aaltomaa-Michalias P, Dahllof A, Lintula M, Nissen E. Newborn behaviour to locate the breast when skin-to-skin: a possible method for enabling early self-regulation. Acta Paediatr. 2011;100(1):79–85. PMID: 20712833. doi: 10.1111/j.1651-2227.2010.01983.x.
44. Charpak N, Ruiz JG, Zupan J, Cattaneo A, Figueroa Z, Tessier R, et al. Kangaroo Mother Care: 25 years after. Acta Paediatr. 2005;94(5):514–522. PMID: 16188735. doi: 10.1111/j.1651-2227.2005.tb01930.x.
45. Charpak N, de Calume ZF, Ruiz JG. "The Bogota Declaration on Kangaroo Mother Care": conclusions at the second international workshop on the method. Second International Workshop of Kangaroo Mother Care. Acta Paediatr. 2000;89(9):1137–1140. PMID: 11071099. doi: 10.1080/713794578.
46. Salim N, Shabani J, Peven K, Rahman QS, Kc A, Shamba D, et al. Kangaroo mother care: EN-BIRTH multi-country validation study. BMC Pregnancy Childbirth. 2021;21(Suppl 1):231. PMID: 33765950. doi: 10.1186/s12884-020-03423-8.
47. Guillen U, Weiss EM, Munson D, Maton P, Jefferies A, Norman M, et al. Guidelines for the Management of extremely premature deliveries: A systematic review. Pediatrics. 2015;136(2):343–350. PMID: 26169424. doi: 10.1542/peds.2015-0542.
48. Raju TNK, Mercer BM, Burchfield DJ, Joseph GF, Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. Obstet Gynecol. 2014;123(5):1083–1096. PMID: 24785861. doi: 10.1097/AOG.0000000000000243.
49. Motojama Y, Namba F, Tan K, Malhotra A. Does Routine Intensive Care Provision at 22–23 Weeks' Gestation Improve Outcomes of Infants Born between 24 and 27 Weeks? Newborn (Clarksville, Md). 2025;4(3):127–132. doi: 10.5005/jp-journals-11002-0132.
50. Kono Y. Neonatal research network of Japan (NRNJ): Prognosis of very low birth weight infants from the database. J Japan Soc Perinat Neonat Med. 2020;56(1):203–212.
51. Isayama T. The clinical management and outcomes of extremely preterm infants in Japan: past, present, and future. Transl Pediatr. 2019;8(3):199–211. PMID: 31413954. doi: 10.21037/tp.2019.07.10.

52. Vidaeff AC, Kaempf JW. The ethics and practice of periviability care. Children (Basel). 2024;11(4). PMID: 38671603. doi: 10.3390/children11040386.
53. Kaempf JW, Moore GP. Extremely premature birth bioethical decision-making supported by dialogics and pragmatism. BMC Med Ethics. 2023;24(1):9. PMID: 36774482. doi: 10.1186/s12910-023-00887-z.
54. Guillen U, Zupancic JAF, Litt JS, Kaempf J, Fanaroff A, Polin RA, et al. Community considerations for aggressive intensive care therapy for infants <24+0 weeks of gestation. J Pediatr. 2024 ;268:113948. PMID: 38336203. doi: 10.1016/j.jpeds.2024.113948.
55. Binepal N, Lemyre B, Dunn S, Daboval T, Aglipay M, Leduc S, et al. Systematic review and quality appraisal of international guidelines on perinatal care of extremely premature infants. Curr Pediatr Rev. 2015;11(2):126–134. PMID: 26050792. doi: 10.2174/1573396311666150608125529.
56. Albersheim S. The extremely preterm infant: Ethical considerations in life-and-death decision-making. Front Pediatr. 2020;8:55. PMID: 32175292. doi: 10.3389/fped.2020.00055.
57. Horbar JD, Greenberg LT, Buzas JS, Ehret DEY, Soll RF, Edwards EM. Trends in mortality and morbidities for infants born 24 to 28 weeks in the US: 1997–2021. Pediatrics. 2024;153(1). PMID: 38053449. doi: 10.1542/peds.2023-064153.
58. Kaempf JW, Guillen U, Litt JS, Zupancic JAF, Kirpalani H. Change in neurodevelopmental outcomes for extremely premature infants over time: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2023;108(5):458–463. PMID: 36270779. doi: 10.1136/archdischild-2022-324457.
59. Rieder TN. Saving or creating: Which are we doing when we resuscitate extremely preterm infants? Am J Bioeth. 2017;17(8):4–12. PMID: 28768134. doi: 10.1080/15265161.2017.1340988.
60. Silverman WA. The Windermere Lecture 1994. The line between 'knowing' and 'doing': medicine's dilemma at the end dilemma at the end of the twentieth century. Arch Dis Child. 1994 ;71(3):261–265. PMID: 7979505. doi: 10.1136/adc.71.3.261.
61. Syltern J, Ursin L, Solberg B, Stoen R. Postponed withholding: Balanced decision-making at the margins of viability. Am J Bioeth. 2022;22(11):15–26. PMID: 33998962. doi: 10.1080/15265161.2021.1925777.
62. Cavolo A, Dierckx de Casterle B, Naulaers G, Gastmans C. Ethics of resuscitation for extremely premature infants: a systematic review of argument-based literature. J Med Ethics. 2020. PMID: 32341186. doi: 10.1136/medethics-2020-106102.
63. Kaempf JW, Dirksen K. Extremely premature birth, informed written consent, and the Greek ideal of sophrosyne. J Perinatol. 2018;38(4):306–310. PMID: 29242573. doi: 10.1038/s41372-017-0024-4.
64. Krizam G, Dongara AR, Khan NA, Derawi H, Raza SM, Ali N, et al. Neonatal tuberculosis in preterm infants admitted to a neonatal intensive care unit in the United Arab Emirates. Newborn (Clarksville, Md). 2025;4(3):138–141. doi: 10.5005/jp-journals-11002-0133.
65. Zhang F, Zhang XF, Zhou HY. Clinical characteristics in 26 children with congenital tuberculosis in Central Southern China: a retrospective study. Paediatr Int Child Health. 2022;42(3-4):127–132. PMID: 37587754. doi: 10.1080/20469047.2023.2246006.
66. Li C, Liu L, Tao Y. Diagnosis and treatment of congenital tuberculosis: a systematic review of 92 cases. Orphanet J Rare Dis. 2019;14(1):131. PMID: 31182120. doi: 10.1186/s13023-019-1101-x.
67. Rajkumar A, Saha SK, Choudhry M. Oral 10% Dextrose was More Effective than Expressed Breast Milk for Pain Relief in Neonates Receiving Their First Dose of Hepatitis B Vaccination. Newborn (Clarksville, Md). 2025;4(3):133–137. doi: 10.5005/jp-journals-11002-0134.
68. Bellieni CV. Neonatal infant pain scale in assessing pain and pain relief for newborn male circumcision. Int J Impot Res. 2023;35(3):282–285. PMID: 35352017. doi: 10.1038/s41443-022-00551-x.
69. Zeltzer LK, Anderson CT, Schechter NL. Pediatric pain: current status and new directions. Curr Probl Pediatr. 1990;20(8):409–486. PMID: 2209068. doi: 10.1016/0045-9380(90)90011-o.
70. Barr RG, Pantel MS, Young SN, Wright JH, Hendricks LA, Gravel R. The response of crying newborns to sucrose: is it a "sweetness" effect? Physiol Behav. 1999;66(3):409–417. PMID: 10357429. doi: 10.1016/s0031-9384(98)00294-7.
71. Jha L, Kumar VN, Banerjee S, Bandhopadhyay C. Efficacy of enhanced dose of expressed breast milk in neonatal procedural pain relief: A randomised placebo-controlled study. Indian J Neonatal Med Res. 2023;11(2):PO01–PO05. doi: 10.7860/IJNMR/2023/59294.2377.
72. Edwards T, Liu G, Battin M, Harris DL, Hegarty JE, Weston PJ, et al. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database Syst Rev. 2022 18;3(3):CD011027. PMID: 35302645. doi: 10.1002/14651858.CD011027.pub3.
73. Singh S, Maheshwari A. Transgenerational epigenetics. Newborn (Clarksville, Md). 2025;4(3):142–152. doi: 10.5005/jp-journals-11002-0137.
74. Bure IV, Nemtsova MV, Kuznetsova EB. Histone modifications and non-coding RNAs: Mutual epigenetic regulation and role in pathogenesis. Int J Mol Sci. 2022;23(10). PMID: 35628612. doi: 10.3390/ijms23105801.
75. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics (Review). Oncol Rep. 2017;37(1):3–9. PMID: 27841002. doi: 10.3892/or.2016.5236.
76. Brehm E, Flaws JA. Transgenerational effects of endocrine-disrupting chemicals on male and female reproduction. Endocrinology. 2019;160(6):1421–1435. PMID: 30998239. doi: 10.1210/en.2019-00034.
77. Schmidt CW. Uncertain inheritance transgenerational effects of environmental exposures. Environ Health Perspect. 2013;121(10):A298–303. PMID: 24218659. doi: 10.1289/ehp.121-A298.
78. Skinner MK, Nilsson EE. Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: Unified Evolution Theory. Environ Epigenet. 2021;7(1):dvab012. PMID: 34729214. doi: 10.1093/eep/dvab012.
79. Fallet M, Blanc M, Di Criscio M, Antczak P, Engwall M, Guerrero Bosagna C, et al. Present and future challenges for the investigation of transgenerational epigenetic inheritance. Environ Int. 2023 ;172:107776. PMID: 36731188. doi: 10.1016/j.envint.2023.107776.
80. Renjith V, Yesodharan R, Noronha JA, Ladd E, George A. Qualitative methods in health care research. Int J Prev Med. 2021;12:20. PMID: 34084317. doi: 10.4103/ijpvm.IJPVM_321_19.
81. More K, Sahni M, Maheshwari A. Systemized systemic sono-screening (S4) protocol: Initial findings. Newborn (Clarksville, Md). 2025;4(3):153–155. doi: 10.5005/jp-journals-11002-0135.
82. Arnold MJ, Jonas CE, Carter RE. Point-of-care ultrasonography. Am Fam Physician. 2020 Mar 1;101(5):275-285. PMID: 32109031.
83. Bersani I, Piersigilli F, Iacona G, Savarese I, Campi F, Dotta A, et al. Incidence of umbilical vein catheter-associated thrombosis of the portal system: A systematic review and meta-analysis. World J Hepatol. 2021;13(11):1802–1815. PMID: 34904047. doi: 10.4254/wjh.v13.i11.1802.
84. Gardin JM, Burn CS, Childs WJ, Henry WL. Evaluation of blood flow velocity in the ascending aorta and main pulmonary artery of normal subjects by Doppler echocardiography. Am Heart J. 1984 ;107(2):310–319. PMID: 6695664. doi: 10.1016/0002-8703(84)90380-6.

85. Pollock JD, Murray IV, Bordes SJ. Physiology, cardiovascular hemodynamics. StatPearls [Internet] [Internet]. 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470310/.
86. Dentali F, Gianni M, Agnelli G, Ageno W. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost. 2008;6(1):70–75. PMID: 17988232. doi: 10.1111/j.1538-7836.2007.02823.x.
87. Vereen RV, Carr N, Puia-Dumitrescu M, Kaempf J, Krick J. Neonatologists' use of social media: A survey exploring professional and personal practices. Newborn 2025;4(3):122–126. doi: 10.5005/jp-journals-11002-0131.
88. Zimba O, Gasparyan AY. Social media platforms: a primer for researchers. Reumatologia. 2021;59(2):68–72. PMID: 33976459. doi: 10.5114/reum.2021.102707.
89. Chen J, Wang Y. Social media use for health purposes: Systematic review. J Med Internet Res. 2021;23(5):e17917. PMID: 33978589. doi: 10.2196/17917.
90. Primack BA, Perryman KL, Crofford RA, Escobar-Viera CG. Social media as it interfaces with psychosocial development and mental illness in transitional-age youth. Child Adolesc Psychiatr Clin N Am. 2022;31(1):11–30. PMID: 34801149. doi: 10.1016/j.chc.2021.07.007.
91. Rao AG, Maheshwari A. Clinical Illustration: Autosomal Recessive Polycystic Kidney Disease. 2025;4(3):156–158. doi: 10.5005/jp-journals-11002-0138.
92. Cadnapaphornchai MA, Dell KM, Gimpel C, Guay-Woodford LM, Gulati A, Hartung EA, et al. Polycystic kidney disease in children: The current status and the next horizon. Am J Kidney Dis. 2025 ;86(3):383–392. PMID: 40113156. doi: 10.1053/j.ajkd.2025.01.022.
93. Subramanian S, Leslie SW, Ahmad T. Autosomal recessive polycystic kidney disease. StatPearls. Treasure Island (FL). 2025.
94. Guo Y, Jain D, Weinreb J. Von Meyenburg Complex: Current Concepts and Imaging Misconceptions. J Comput Assist Tomogr. 2019;43(6):846–851. PMID: 31356525. doi: 10.1097/RCT.0000000000000904.
95. Levy AD, Rohrmann CA, Jr, Murakata LA, Lonergan GJ. Caroli's disease: radiologic spectrum with pathologic correlation. AJR Am J Roentgenol. 2002;179(4):1053–1057. PMID: 12239064. doi: 10.2214/ajr.179.4.1791053.

SURVEY

Kangaroo Care—Knowledge, Attitude, and Practices among Clinicians: International Perspective from a Cross-sectional Survey

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Abstract

Introduction: Kangaroo care (KC) is a low-cost, effective intervention offering many benefits to the infant, parents, health system, and society. Although knowledge, attitudes, and practices (KAP) regarding KC among clinicians have reported at a single-institution or local regional levels, concerns remain about information gaps related to national income levels. This study aimed to explore disparities in KAP on KC among clinicians across countries with different income levels.

Methods: A web-based survey was conducted between December 2024 and March 2025. Only one response per clinician was collected.

Results: Responses from 134 clinicians across 32 countries revealed that while awareness and acceptance of KC were generally high among caregivers and parents, significant disparities existed based on country income levels. Most respondents (90%) reported acceptable knowledge levels, but formal training for caregivers was limited (36%), particularly in upper-middle-income countries (UMICs). Local guidelines were more commonly available in lower-middle-income countries (LMICs) than in UMICs. Attitudes toward KC were largely positive among both caregivers (84%) and parents (78%), with higher support observed in high-income countries (HICs). Mothers often preferred practicing KC with their partner present and generally felt comfortable during the process. In practice, KC was more widely implemented for both term and preterm infants in HICs, whereas LMICs focused more on preterm or low birth weight infants.

Conclusions: There is a need for more structured training and consistent guidelines to promote equitable and effective KC practices globally.

Keywords: Attitude, Income level, Kangaroo care, Knowledge, Low-birth-weight infant, Practices, Preterm infant, Survey, Term infant.

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Introduction

Kangaroo care (KC), also known as kangaroo mother care (KMC), is a simple, low-cost, and effective intervention with immense benefits for infants, especially those born preterm (<37 weeks' gestation) and/or low birth weight (<2,500 gm), family, healthcare system, and society at large.[1,2]

Existing literature on knowledge, attitudes, and practices (KAP) is mainly limited to either single-institutional or regional studies. These studies have identified several barriers to effective KC implementation, such as limited caregiver and parental awareness, poor human resources, and limited infrastructure.[3,4] Some researchers have reported that improvements in knowledge and behavior helped increase the adoption and earlier initiation of KMC in ventilated, extremely preterm infants.[5]

The World Health Organization (WHO) endorses KMC as a proven strategy for improving care and outcomes of low-birth-weight infants.[6] Notably, immediate KMC, compared to initiation of KMC after stabilization, improved survival in infants with birth weights between 1,000 gm and 1,799 gm, reducing mortality by 25%.[7] However, even though institutional and/or regional successes are encouraging, the proven effectiveness of KMC warrants a coordinated international effort to facilitate its widespread adoption. An important unanswered question is whether (KAP) for KMC differ by country income levels. This study aims to address this gap in implementation of KMC.

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Methods

Clinicians providing care to preterm and full-term infants were identified from the Global Newborn Society members list. They were then contacted by e-mail or through a messaging application such as WhatsApp. The Global Newborn Society is a globally active, well-recognized, registered non-profit organization (EIN: 86-358640; https://www.globalnewbornsociety.org/) registered in the United States. The organization is focused on promoting the health of newborn infants. They currently support efforts in 138 countries and has more than 10,000 members; they seek to promote relevant research into the epidemiology, including risk factors and burden of disease, and pathophysiology of disease; training healthcare workers; and seek social engagement.

Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA) was used to create a secure e-questionnaire and capture the responses. A questionnaire was drafted, piloted, and refined before its distribution to the participants. The link to access the questionnaire was included in the request-to-participate letter. Most questions were closed ones (either single or multiple-choice), with one open-ended question allowing free-text descriptions of KMC practices. Ethical approval was obtained from the Local Institutional Review Board before commencing the study. Information regarding the purpose of the study, names of the investigators, informed consent process, time for completion of the survey, security of data storage, and protection of participants' privacy was provided in the request-to-participate invitation letter. Participation in the survey was voluntary, and participants consented by proceeding with the survey. Only one response per NICU was requested. To increase participation in the survey, a reminder was sent twice after the initial invitation. Survey-related biases were reduced by following the checklist for reporting results of internet e-surveys.[8]

Statistics

Data were analyzed using Stata 17 (StataCorp, College Station, TX, USA). Descriptive statistics were used to summarize the responses. The Chi-squared test, or Fisher's exact where appropriate, was used to explore income status-based differences in KC practices.

Results

Responses were received from 134 NICUs across 32 countries. The highest proportion of responses was from high-income countries HIC, 71 (54%), followed by 34 (26%) from upper-middle-income countries (UMIC) and 25 (20%) from lower-middle-income countries (LMIC). Two participants did not report the name of their country. The World Bank assigns each country to one of the four groups: Low, lower middle, upper-middle, and high-income countries based on its economic performance. We used the current World Bank report to reflect the income status category of the participating unit's country. Tables 1 and 2 summarize the responses of the care providers for the overall cohort and by country income level, respectively.

Knowledge

Most respondents reported that the level of knowledge of KMC at their hospital was acceptable (120/134, 90%). Formal training on KMC to caregivers was available in only 48 of the 134 hospitals (36%), with the lowest availability in UMICs (7/34, 21%). Working in, or having worked in, a hospital that practices KC was the most common training resource (53/134, 40%). No training whatsoever was reported by 13/134 (10%) participants, with the highest proportion from UMICs (9/34, 26%). Most hospitals reported having a local guideline for KMC; however, availability varied significantly by income setting. Guideline availability was highest in LMIC hospitals (24/27, 89%) and lowest in UMIC hospitals (15/34, 44%).

Attitudes

Nearly two-thirds of parents had no prior awareness of KMC but were willing to learn and practice it after childbirth. Most caregivers perceived that KMC offered many benefits to the infant and family, with enhanced bonding between the mother and baby being the most cited benefit. However, there was variation in the perceived benefits to the parents – enhanced bonding between the mother and baby was the most reported benefit, while improved neurodevelopment was the least perceived (Fig. 1). Overall, caregivers had a positive attitude toward KMC (110/131, 84%) – with the highest proportion in HICs (65/69, 94%). The rates were lower in both LMICs and UMICs (just over 70%). Parents also had an equally positive attitude toward KMC (102/130, 78%) – showing a similar trend by income setting as seen among caregivers. Most mothers preferred doing KC in the presence of their husband/partner (104/130, 80%) – however, this varied by region from 87% in HICs to 70% in UMICs. Most mothers did not feel uncomfortable keeping their chest bare during KC (94/132, 71%). Caregivers perceived that mothers felt the most uncomfortable in HICs (23/70, 33%) and the least uncomfortable in LMICs (6/27, 22%).

Practices

Kangaroo mother care was commonly practiced for both full-term and preterm infants; however, nearly a third of hospitals offered it only to preterm or low birth weight infants. There was also

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Table 1: Care providers' responses on KAP for KC

Questions	*Response options*	*Response rate expressed as number (percentage)*
How would you rate the level of knowledge of KC at your hospital? (*n* = 134)	Excellent	45 (34%)
	Very good	50 (37%)
	Good	25 (19%)
	Average	10 (7%)
	Poor	4 (3%)
What training do caregivers receive on KC at your hospital? (*n* = 134)	Formal training on KC	48 (36%)
	Worked or is working in a hospital that practices KC	53 (39%)
	Access to educational materials on KC	20 (15%)
	No training whatsoever	13 (10%)
Does your hospital have a practice guideline on KC? (*n* = 133)	Yes	100 (75%)
	No	33 (25%)
What is the level of awareness of mothers on KC at your hospital? (*n* = 134)	They are well aware of the antenatal period	46 (34%)
	No prior awareness, but willing to learn and practice KC after childbirth	85 (64%)
	No prior awareness and NOT willing to learn or practice KC after childbirth	3 (2%)
What is the level of awareness of fathers on KC at your hospital? (*n* = 134)	They are well aware from the antenatal period	40 (30%)
	No prior awareness but willing to learn and practice KC after childbirth	82 (61%)
	No prior awareness and NOT willing to learn or practice KC after childbirth	12 (9%)
What infants receive KC at your hospital? (*n* = 134)	Only full-term babies	5 (4%)
	Only preterm or low birth weight babies	42 (31%)
	Both full-term and preterm/low birth weight babies	87 (65%)
For the following scenarios, do preterm or low birth weight babies receive KC at your hospital? (*n* = 81)	If they are intubated	36 (44%)
	If they have umbilical catheters	12 (15%)
	If they are not well	33 (41%)
When do term infants receive KC at your hospital? (*n* = 131)	Immediately after birth	62 (47%)
	On the first day after birth	14 (11%)
	In the first week after birth	15 (12%)
	From the second week after birth	3 (2%)
	Only when a baby is stable	37 (28%)
When do preterm or low birth weight infants receive KC at your hospital? (*n* = 101)	Immediately after birth	19 (19%)
	On the first day after birth	12 (12%)
	In the first week after birth	20 (20%)
	From the second week after birth	5 (5%)
	Only when a baby is stable	45 (46%)
When do extremely preterm or extremely low birth weight infants receive KC at your hospital? (*n* = 102)	Immediately after birth	10 (10%)
	On the first day after birth	4 (4%)
	In the first week after birth	24 (23%)
	From the second week after birth	4 (4%)
	Only when a baby is stable	60 (59%)
When do micro preterm (≤23 weeks gestation) or ultra-low birth weight infants (<500 gm at birth) receive KC at your hospital? (*n* = 101)	Immediately after birth	2 (2%)
	On the first day after birth	5 (5%)
	In the first week after birth	12 (12%)
	From the second week after birth	6 (6%)
	Only when a baby is stable	76 (75%)

(Contd...)

Table 1: *(Contd...)*

Questions	*Response options*	*Response rate expressed as number (percentage)*
Do caregivers at your hospital have a positive attitude toward KC in sick/unstable infants? (*n* = 131)	Yes	110 (84%)
	No	21 (16%)
Do parents at your hospital have a positive attitude toward KC in sick/unstable infants? (*n* = 130)	Yes	102 (78%)
	No	28 (22%)
Do mothers at your hospital prefer to do KC in the presence of their husband/partner? (*n* = 130)	Yes	104 (80%)
	No	26 (20%)
Do mothers at your hospital feel uncomfortable keeping their chests bare during KC and therefore avoid KC? (*n* = 132)	Yes	38 (29%)
	No	94 (71%)
Who are the main sources of support at your hospital for parents on KC? (*n* = 134), multiple responses allowed	Caregivers	110 (82%)
	Husband/partner	25 (26%)
	Family members	18 (13%)
	None	5 (4%)

considerable variation by income setting. Kangaroo mother care for term and preterm or low birth weight infants was practiced in most HIC hospitals (60/71, 85%) and least in LMIC hospitals (7/27, 26%), where it was primarily offered to preterm or low birth weight infants 20/27, 74%). Kangaroo care was uncommon for preterm or low birth weight infants who were intubated, had umbilical catheters *in situ*, or were unwell. Hospitals in HICs were more likely to practice KC in intubated preterm infants than in those who were unwell infants or those with umbilical catheters *in situ*. Regarding timing, less than half of the participating hospitals were offering KC immediately after birth. Hospitals in UMICs and LMICs preferred to wait until the infant was stable before performing KMC. Only 19% hospitals performed KMC immediately after birth, compared to 47% of hospitals that offered it in term infant units. For extremely or micro-preterm infants and/or extremely low or ultra-low birth weight infants, most hospitals waited until infants were stable. Caregivers were the most common resource for supporting parents with KMC, followed by husband/partner and other family members.

Discussion

This international survey demonstrated that awareness and acceptance of KMC were generally high among caregivers and parents, but significant variations exist based on country income levels. Most respondents (90%) reported acceptable knowledge levels; however, training for caregivers was often informal. There were limited formal training opportunities, particularly in UMICs. Local guideline availability varied by income setting and was more common in LMICs than in UMICs. Attitude toward KMC was generally positive among both caregivers (84%) and parents (78%), with higher support observed in HICs. Mothers often preferred performing KMC with their husband/partner present and generally felt comfortable during the process. In practice, income setting-based variation exists, HICs widely implemented KMC for both term and preterm infants, whereas LMICs focused more on preterm or low birth weight infants. Initiation of KMC after birth was often delayed, especially in UMICs and LMICs. Instability of the infant was often a barrier to practicing KMC. Caregivers played a central role in supporting parents.

Kangaroo mother care provides many benefits to the infant, family, and society. It reduces infant mortality and morbidity, improves infant growth and development, increases rates of breastfeeding, and reduces hospital stay.[9] The World Health Organization (WHO) recommends this intervention as the standard of care for preterm or low birth weight infants.[7] Previous studies have reported on knowledge, attitudes, and practice of KC at either the single-institution or regional level.[3,4] Building on this evidence, our survey, provides a unique insight from clinicians in different income-based settings. Our findings align with some findings reported in a recent systematic review, showing that knowledge and acceptance of KC among caregivers and parents was high, variation in formal or informal caregiver training on KC, limited prior parental knowledge but willingness to learn and engage in performing KMC after childbirth, and uncertainty on infant's eligibility based on gestational age and sickness and timing after birth.[9]

We observed disparities between caregivers' perceptions of the benefits of KMC for the parents and those reported in the literature – caregivers in our survey reported lower parental perception of benefits, especially on the neurodevelopmental outcomes. An interesting finding was that modesty concerns in the mother (keeping the chest bare) and the presence of a partner/husband were not considered barriers to implementing KMC.

The strength of this study was representative participation from diverse income settings; therefore, the findings are generalizable to a wider neonatal community. Our study has certain limitations. The questionnaire was prepared only in the English language, which may have excluded participation from NICUs in non-English speaking regions. Additionally, only clinicians, not parents, participated in this survey.

In conclusion, this survey highlights the need for more structured training and consistent guidelines to promote equitable and effective KC practices globally. Future studies could explore parental and clinicians (KAP) regarding KMC across all six WHO regions.

Table 2: Care providers' responses on knowledge, attitude, and practices for KC responses by country income levels

Question	*Response options*	*Response rate expressed as number (percentage)*			*p-value*
		HICs	*UMICs*	*LMICs*	
What training do caregivers receive on KC at your hospital? (*n* = 132)	Formal training on KC	29/71 (41%)	7/34 (21%)	12/27 (44%)	0.003
	Worked or working in a hospital that practices KC	26/71 (37%)	16/34 (47%)	9/27 (33%)	
	Access to educational materials on KC	13/71 (18%)	2/34 (6%)	5/27 (19%)	
	No training whatsoever	3/71 (4%)	9/34 (26%)	1/27 (4%)	
Does your hospital have a practice guideline on KC? (*n* = 133)	Yes	60/70 (86%)	15/34 (44%)	24/27 (89%)	<0.001
	No	10/70 (14%)	19/34 (56%)	3/27 (11%)	
What is the level of awareness of mothers on KC at your hospital? (*n* = 134)	They are well aware from the antenatal period	36/71 (51%)	5/34 (15%)	5/27 (19%)	<0.001
	No prior awareness but willing to learn and practice KC after childbirth	35/71 (49%)	26/34 (76%)	22/27 (81%)	
	No prior awareness and NOT willing to learn or practice KC after childbirth	0	3/34 (9%)	0	
What is the level of awareness of fathers on KC at your hospital? (*n* = 134)	They are well aware from the antenatal period	31/71 (44%)	5/34 (14%)	4/27 (15%)	0.002
	No prior awareness but willing to learn and practice KC after childbirth	38/71 (54%)	23/34 (68%)	19/27 (70%)	
	No prior awareness and NOT willing to learn or practice KC after childbirth	2/71 (2%)	6/34 (18%)	4/27 (15%)	
What infants receive KC at your hospital? (*n* = 134)	Only full-term babies	3/71 (4%)	2/34 (6%)	0	<0.001
	Only preterm or low birth weight babies	8/72 (11%)	13/34 (38%)	20/27 (74%)	
	Both full-term and preterm/low birth weight babies	60/71 (85%)	19/34 (56%)	7/27 (26%)	
When do term infants receive KC at your hospital? (*n* = 131)	Immediately after birth	45/70 (64%)	10/34 (29%)	7/26 (27%)	0.001
	On the first day after birth	9/70 (13%)	1/34 (3%)	3/26 (12%)	
	In the first week after birth	5/70 (7%)	7/34 (21%)	3/26 (12%)	
	From the second week after birth	1/70 (1%)	1/24 (3%)	1/26 (3%)	
	Only when a baby is stable	10/70 (15%)	15/34 (44%)	12/26 (46%)	
When do preterm or low birth weight infants receive KC at your hospital? (*n* = 101)	Immediately after birth	12/48 (25%)	5/28 (18%)	2/24 (8%)	NS
	On the first day after birth	8/48 (17%)	1/28 (4%)	3/24 (13%)	
	In the first week after birth	10/48 (21%)	5/28 (18%)	4/24 (17%)	
	From the second week after birth	1/48 (2%)	4/28 (14%)	0/24	
	Only when a baby is stable	17/48 (35%)	13/28 (46%)	15/24 (63%)	
When do extremely preterm or extremely low birth weight infants receive KC at your hospital? (*n* = 102)	Immediately after birth	6/48 (13%)	2/28 (7%)	2/25 (8%)	NS
	On the first day after birth	4/48 (8%)	0/28	0/25	
	In the first week after birth	14/48 (29%)	4/28 (14%)	5/25 (20%)	
	From the second week after birth	2/48 (4%)	1/28 (4%)	1/25 (4%)	
	Only when a baby is stable	22/48 (46%)	21/28 (75%)	17/25 (68%)	

(Contd...)

Table 2: *(Contd...)*

Question	*Response options*	*Response rate expressed as number (percentage)*			*p-value*
		HICs	*UMICs*	*LMICs*	
When do micro preterm (≤23 weeks gestation) or ultra-low birth weight infants (<500 gm at birth) receive KC at your hospital? (*n* = 101)	Immediately after birth	2/48 (4%)	0/28	0/24	NS
	On the first day after birth	4/48 (8%)	1/28 (4%)	0/24	
	In the first week after birth	9/48 (19%)	1/28 (4%)	1/24 (4%)	
	From the second week after birth	4/48 (8%)	2/28 (7%)	0/24	
	Only when a baby is stable	29/48 (61%)	24/28 (85%)	23/24 (96%)	
Do caregivers at your hospital have a positive attitude toward KC in sick/unstable infants? (*n* = 131)	Yes	65/69 (94%)	25/34 (74%)	19/27 (70%)	0.003
Do parents at your hospital have a positive attitude toward KC in sick/unstable infants? (*n* = 130)	Yes	63/69 (91%)	21/34 (62%)	17/26 (65%)	0.001
Do mothers at your hospital prefer to do KC in the presence of their husband/partner? (*n* = 130)	Yes	60/69 (87%)	23/33 (70%)	20/27 (74%)	NS
Do mothers at your hospital feel uncomfortable keeping their chests bare during KC and therefore avoid KC? (*n* = 132)	Yes	23/70 (33%)	9/34 (26%)	6/27 (22%)	NS
Who are the main sources of support at your hospital for parents on KC? (*n* = 134), multiple responses allowed	Caregivers	62/71 (87%)	25/34 (74%)	23/27 (85%)	NS
	Husband/partner	22/71 (31%)	7/34 (21%)	6/27 (22%)	
	Family members	7/71 (10%)	4/34 (12%)	6/27 (22%)	
	None	0	4/34 (12%)	1/27 (4%)	

NS = $p > 0.05$

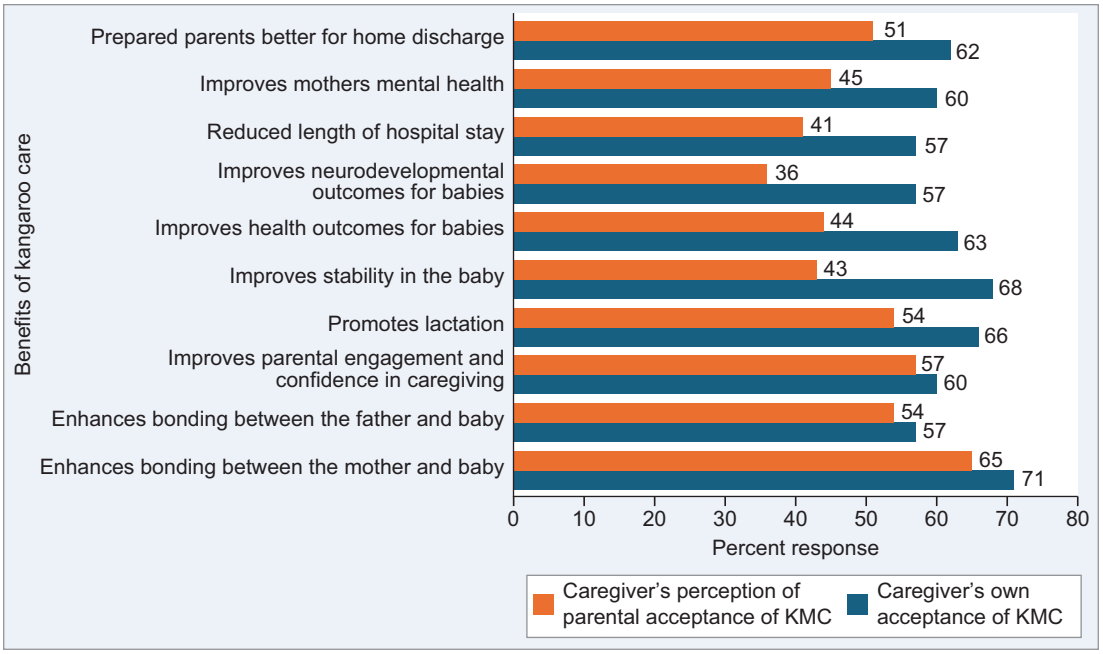

Fig. 1: Histogram

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References

1. Boundy EO, Dastjerdi R, Spiegelman D, et al. Kangaroo mother care and neonatal outcomes: A meta-analysis. Pediatrics 2016;137(1):e20152238. DOI: 10.1542/peds.2015-2238.
2. Moore ER, Bergman N, Anderson GC, et al. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev 2016;11(11):CD003519. DOI: 10.1002/14651858.CD003519.pub4.
3. Chugh Sachdeva R, Mondkar J, Shanbhag S, et al. A qualitative analysis of the barriers and facilitators for breastfeeding and kangaroo mother care among service providers, mothers and influencers of neonates admitted in two urban hospitals in India. Breastfeed Med 2019;14(2):108–114. DOI: 10.1089/bfm.2018.0177.
4. Shah RK, Sainju NK, Joshi SK. Knowledge, attitude and practice towards kangaroo mother care. J Nepal Health Res Counc 2017;15(3):275–281. DOI: 10.33314/jnhrc.v15i3.1173.
5. Cooper L, Morrill A, Russell RB, et al. Close to me: Enhancing kangaroo care practice for NICU staff and parents. Adv Neonat Care 2014;14(6):410–423. DOI: 10.1097/ANC.0000000000000144.
6. Darmstadt GL, Kirkwood B, Gupta S, et al. WHO Global Position Paper and Implementation Strategy on kangaroo mother care call for fundamental reorganisation of maternal–infant care. Lancet 2023;401(10390):1751–1753. DOI: 10.1016/S0140-6736(23)01000-0.
7. WHO Immediate KMC Study Group. Immediate "kangaroo mother care" and survival of infants with low birth weight. N Engl J Med 2021;384(21):2028–2038. DOI: 10.1056/NEJMoa2026486.
8. Eysenbach G. Improving the quality of Web surveys: The checklist for reporting Results of Internet E-surveys (CHERRIES). J Med Internet Res 2004;6(3):e34. DOI: 10.2196/jmir.6.3.e34.
9. Almutairi A, Gavine A, McFadden A. Parents' and healthcare providers' perceptions, experiences, knowledge of, and attitudes toward kangaroo care of preterm babies in hospital settings: Mixed-methods systematic review. Birth 2024;51(4):690–707. DOI: 10.1111/birt.12859.

ORIGINAL RESEARCH

Neonatologists' Use of Social Media: A Survey Exploring Professional and Personal Practices

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Abstract

Background: Limited data specifically describe how physicians utilize social media for professional purposes, with some studies suggesting differences based on specialty and demographics. This study explored how neonatologists use social media and its impact on their clinical practice, given the growing use of social media for health information.

Methods: An anonymous online survey was distributed to neonatologists through the American Academy of Pediatrics (AAP) Section on Neonatal and Perinatal Medicine.

Results: A total of 223 neonatologists participated in the survey. The majority reported that they "Never" or "Rarely" contribute to (74%), seek (68%), or scan (58%) social media for medical knowledge. Opinions on the impact of social media on clinical practice were mixed, with perceptions varying significantly by age (p-value < 0.01). Those who viewed social media positively highlighted its role in increasing awareness of recent publications and providing valuable parental insights. Conversely, the most common concern was the potential for misinformation, bias, and confusion stemming from social media content.

Conclusions: Although most neonatologists "Never/Rarely" use social media to contribute or seek medical information, a notable proportion are scanning social media platforms to stay informed about recent publications and potentially enhance the quality of care. Older neonatologists and those with more experience perceive social media as less valuable and less positively impacting clinical care. It is likely neonatologists are not using social media at the same rate as families, which could contribute to communication gaps as families increasingly use social media for information and support. Further research is needed to assess the effects of social media on healthcare quality and resource allocation and to develop strategies to mitigate misinformation and confusion.

Keywords: Misinformation, Neonatology, Patient communication, Patient education, Social media.

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Key Points

- This study found low social media engagement amongst neonatologists, with 74% rarely or never contributing content.
- Younger neonatologists (≤50 years) view social media's professional impact more positively, while older practitioners are more negative.
- Key barriers to social media use include concerns about misinformation, time burden, confidentiality, and professional/legal issues.
- Neonatologists' limited social media engagement represents a missed opportunity to provide reliable information and support to NICU families who increasingly seek health information online.

Introduction

The impact of social media on patient communication, education, and clinical practice has rapidly grown due to exponentially increasing platforms, accessibility, and ease of dissemination.[1–3] Physicians, professional organizations, and healthcare journals use various platforms for networking, education, organizational promotion, and patient education.[1,3] Previous surveys have described that over 90% of physicians use social media for personal or professional purposes.[4–6] Approximately 1/3 of physicians interact with patients and families via social media, yet a minority of physicians actively comment or post content.[7,8] Limited data specifically describe how physicians utilize social media for professional purposes, with some studies suggesting differences based on specialty and demographics.[8]

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Pediatricians were early adapters of social media. "Tweetiatricians," or pediatricians who use "X" (formerly Twitter), utilize social media to disseminate information, publicize medical recommendations, promote children's health, counteract online misinformation, and connect with other practitioners.[9] Pediatricians commonly utilize social media for child health advocacy, particularly

legislation and health campaigns.[10] They also tend to interact more with patients and families than non-pediatric physicians.[7] Previous studies suggest that most parents use social media to access health information, with parents of young children using it more frequently than parents of older children.[11] Higher utilization of social media among early-career physicians is likely related to more familiarity with newer technologies, previous mentoring, and conference attendance, where social media sharing has been encouraged.[8] The American Academy of Pediatrics (AAP) encourages all pediatricians to increase their knowledge of digital technology to enhance the utilization of social media tools that their patients and families use (e.g., to support timely anticipatory media guidance).[12] The AAP Committee on Bioethics and the Committee on Medical Liability and Risk Management have published clinical reports and guidelines on the ethical use of social media and toolkits for practical use.[13,14]

The neonatology community is considered relatively active in digital technologies and social media; still, there needs to be more data on how the community is actively utilizing social media.[10] Previous studies report the growing use of social media amongst neonatologists, specifically in building a community of practice or a community that "shares knowledge and builds collaborative networks across disciplines, institutions, and countries."[15] However, no studies have quantified social media use or explored attitudes toward its use among neonatologists. This study aims to describe neonatologists' utilization, interactions with, and attitudes towards social media, specifically for education and effective quality of care, and to inform future advocacy and educational targets for neonatologists practicing in an ever-connected world. We also evaluate basic physician demographics associated with social media use.

Methods

The survey was informed by published, validated instruments that assess technology acceptance.[16] It measured perceived usefulness, ease of use, and how these factors influence attitudes, intentions, and acceptance of social media. Several questions assessed agreement with statements such as "I find social media easy to use" and "Using social media helps improve the quality of my patient care" with a 5-point Likert scale. Primary demographic data and details on social media usage were also gathered (Supplementary Material). This voluntary survey did not collect any personal or institutional identifiers. The University of Utah Institutional Review Board approved the study as exempt.

Recruitment

The 21-question survey was distributed to neonatal providers via the AAP Section on Neonatal and Perinatal Medicine (SONPM) listserv and through social media advertisement. With approximately 3,500 members in SONPM and based on response rates from previous surveys using the same listserv, an estimated 5–15% response rate was anticipated, equating to about 150–525 responses.[17–20]

Statistics Analysis

Data analysis included descriptive statistics to summarize responses to the survey. For analysis by age, respondents were separated into "younger" (≤50 years) and "older" (>50 years) groups to obtain similar group sizes. Responses to questions utilizing a 5-point Likert scale were grouped into agreement, disagreement, or neutral, consistent with the original use of the adapted scale.[16] A Chi-square analysis was conducted to evaluate whether various demographics were associated with different responses.

Table 1: Respondent demographics

Demographic	*Total, n = 223 (%)*		
Gender		**Years in practice**	
Male	80 (36)	Current trainee	17 (8)
Female	134 (60)	<5 years	28 (13)
Other/prefer not to answer	9 (4)	5–10 years	36 (16)
		11–15 years	31 (14)
Age		16–20 years	28 (13)
<41 years	65 (29)	>20 years	81 (36)
41–50 years	53 (24)		
51–60 years	45 (20)	**Group size**	
>60 years	54 (24)	<10	77 (35)
		10–20	71 (32)
Primary practice type		>20	63 (28)
Academic	154 (69)		
Private practice	48 (22)		
Military	15 (7)		
Other	12 (5)		

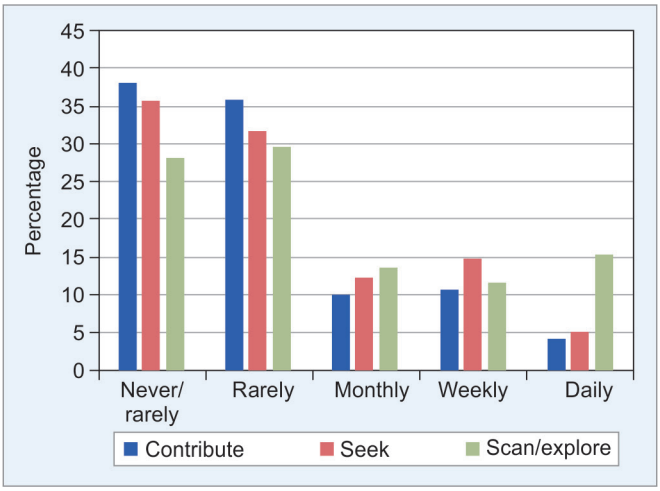
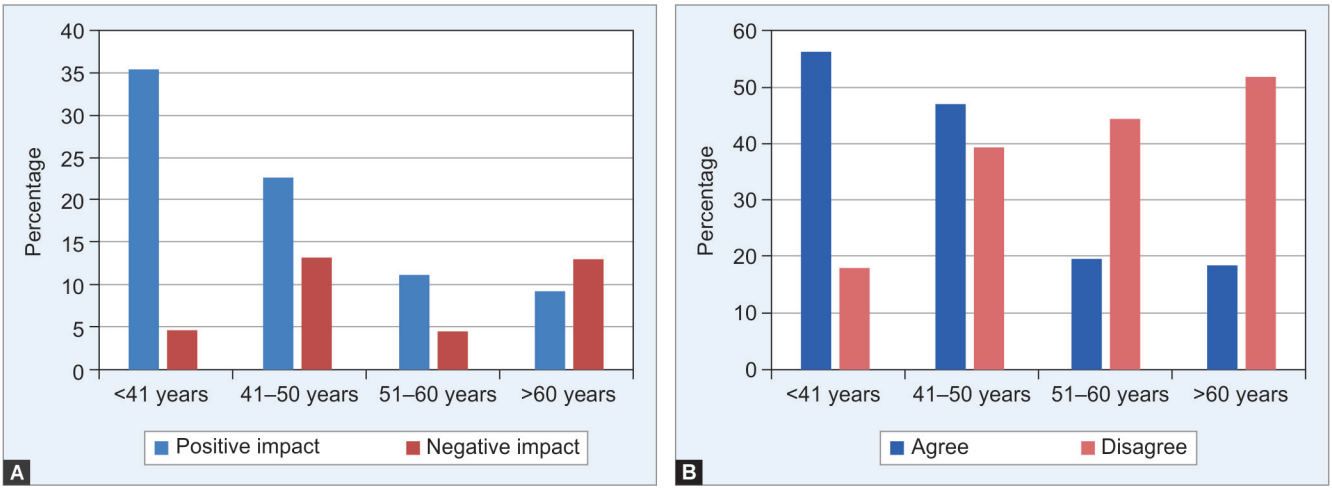


Fig. 1: Reported frequence of using social media to contribute medical knowledge, seek specific information, or scan/explore medical knowledge

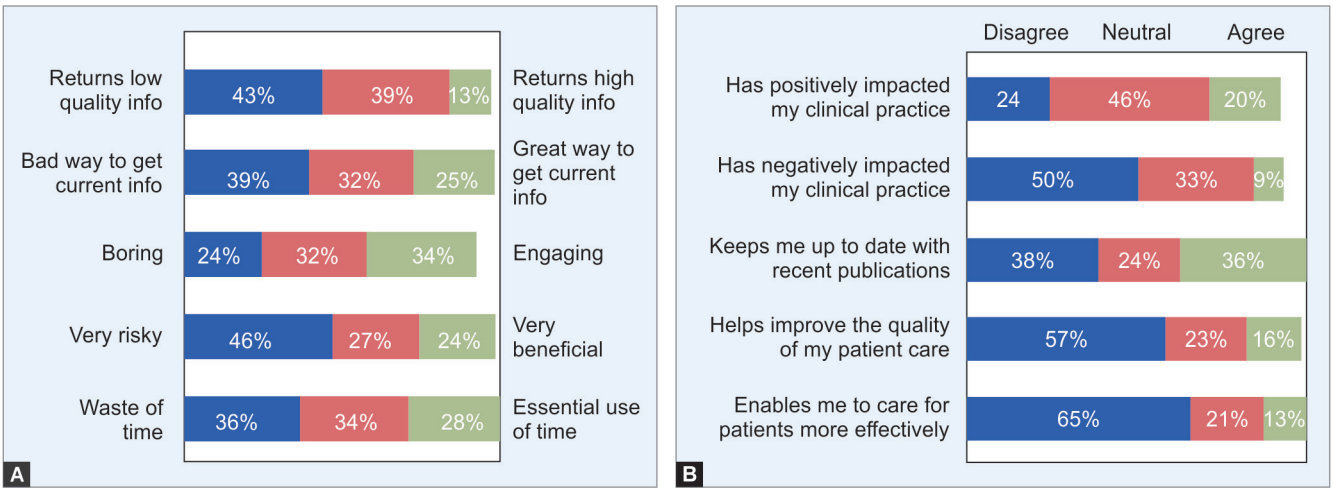
Results

The survey, conducted between July and August 2023, received 223 responses, representing a 6.4% response rate. Most respondents were female (60%) and worked in academic institutions (67%) (Table 1). Most reported "Never" or "Rarely" contributing to (74%), seeking (68%), or scanning (58%) social media for medical knowledge. About one-third of respondents use social media at least once a month. While 43% use social media solely to view medical information, 23% view and share content (Fig. 1). In addition, 21% reported no social media use. Usage varied across platforms, with LinkedIn and Facebook being the most popular.

Younger practitioners (≤50 years) more positively view social media's impact on clinical practice, while older practitioners (>50 years) lean towards a more negative perspective (p-value < 0.01, Fig. 2). Additionally, younger age was associated with viewing social media as an effective way to stay updated with recent, relevant



Figs 2A and B: (A) Perceived impact of social media on clinical practice, categorized by age-groups; (B) Respondents reported the impact of social media on keeping up to date



Figs 3A and B: (A) Attitudes of respondents towards various aspects of social media, categorized by level of agreement; (B) Attitudes of respondents towards the impact of social media on their clinical practice and patient care, categorized by level of agreement

publications (p-value < 0.01, Fig. 2). Specific positive impacts of social media cited by respondents included access to educational podcasts, increased awareness of timely articles, exposure to diverse perspectives from various experience levels and geographic areas, better access to parental viewpoints, crowdsourcing for challenging cases, awareness of new or evolving practices, resources beyond their practice center, access to leaders in the field, and connections with NICU graduates and families.

Negative aspects highlighted included families receiving unrealistic or incorrect information, the unrecognized time burden of social media, the spread of dangerous myths and misinformation, negative comments about doctors, NICUs, or clinics, and conflicting or confusing information for parents. No statistically significant associations were found between social media use or views on social media and factors such as practice type (academic vs private), practice size, or gender.

Respondents were asked to evaluate their attitudes toward social media across five dimensions: Overall usefulness, riskiness, engagement, usefulness for obtaining current information, and quality of information (Fig. 3). The majority expressed negative or neutral views on these aspects. Most respondents disagreed or were neutral about social media's role in enhancing their ability to care for patients or improving the quality of care they provide (Fig. 3).

When asked about sharing resources with parents, respondents were more likely to provide handouts created by their organization (75%) or external sources (61%), as well as recommend websites with medical information (55%) and websites of parent support organizations (63%). They were significantly less likely to share social media accounts with medical information (11%) or social media groups for NICU parents (24%).

Regarding engagement with parents through social media, 22% of respondents reported not using social media, and 53% did not communicate with NICU parents via these platforms—only 20% accepted friend requests from parents, and 15% engaged in discussions about medical knowledge.

Discussion

Our survey of neonatologists reveals varied use and attitudes toward social media for professional purposes. Younger practitioners (≤50 years) use social media more frequently and report positive impacts

on their clinical practice. In contrast, many respondents avoid social media due to concerns about disinformation. Consistent with previous surveys of physicians, few neonatologists actively contribute to online healthcare content.[16,21–23]

Neonatologists' attitudes toward social media appear more negative than those in other specialties.[16] Respondents cited institutional and time constraints as barriers to social media use. These findings are consistent with previous surveys, highlighting physicians' hesitations about social media due to concerns about confidentiality, professionalism, misinformation, and legal issues.[24] This presents an opportunity for institutions to develop social media engagement training programs to foster effective and active participation.[22,24]

Respondents highlighted several positive aspects of social media, including valuable educational content and online academic communities facilitated through educational podcasts, updates on recent articles, sharing of resources and protocols, and access to field leaders.[15,25,26] This aligns with previous research where physicians used social media to stay current.[16,24] Younger neonatologists and parents of young children engage with social media more frequently than their older counterparts.[8,11,27] These positive aspects of social media represent areas that would likely be more readily accepted by a broader audience in the field, thus representing a future target for educational offerings and advocacy for neonatal leaders.

Survey respondents expressed concerns about general misinformation, the uncompensated workload associated with social media engagement with families, the spread of dubious or dangerous myths, undue criticism of doctors, NICUs, and clinics, and conflicting or confusing posts. Misinformation and disinformation are significant issues within social media dynamics. For example, false profiles and bots propagate poor-quality, uncertain, or fabricated information about vaccines and substance use, contributing to vaccine hesitancy and the promotion of substance use.[28,29] Additionally, the traditional measure of physician workload through relative value units may only partially reflect the time and resources dedicated to social media.[30] University-based physicians, who also handle research and teaching duties, highlight the need for more research to accurately capture the workload of neonatologists, define workload appropriately, and allocate correct full-time equivalents (FTE).[30,31] Active engagement and promotion of educational content over social media may be considered less traditional methods of advancing the field—still, they may represent efforts deserving of dedicated and protected work time in the future.

Our survey indicates potential opportunities to enhance neonatologists' communication with families through online tools and social media. The AAP advocates for improving digital literacy and appropriate social media use, acknowledging that parents and families increasingly rely on social media for health information.[11,27] NICU families increasingly turn to social media for healthcare decision support, obtaining health information, seeking anticipatory guidance, and sharing emotional support. This underscores the importance for neonatologists to engage effectively and ensure their presence is accurate, accessible, and reliable.[27,32,33]

Parents primarily use social media to seek and share support, find valuable medical information, and reassure themselves about NICU decisions made with physicians.[34] Previous reports indicate that some families prefer health information from online sources, believing that other NICU families are more familiar with caregiving challenges and self-management strategies than healthcare professionals.[34] Neonatologists' limited use of social media and lack of engagement in creating meaningful content may represent a missed opportunity to provide NICU families with reliable and accessible resources and advice. Further quantitative and qualitative research is needed to examine parental attitudes, physician participation, resource utilization, and the expanding role of social media and online platforms in enhancing NICU quality, safety, and satisfaction.

The principal limitation of our survey is the low response rate of 6.4%, yet consistent with previous SONPM surveys.[17–20] There is conceivably selection bias from respondents and non-respondents who have variable use of social media, including positive or negative experiences, which could constrain the heterogeneity of responses. We also restricted the number of questions to facilitate participation, recognizing that the breadth and depth of our investigation are limited. In addition, the generalizability of the findings here is specific to neonatologists targeted by the survey.

Conclusions

This study highlights a significant gap in social media engagement among neonatologists. Younger practitioners have a more positive outlook and are more active on social media, while older practitioners often have concerns about misinformation and professionalism. Despite these concerns, social media offers a potential avenue for increased engagement with other field members through informal conversation and sharing of the latest information, and a potential target for future educational efforts. In addition, social media offers valuable opportunities for enhancing communication with NICU families, who increasingly use these platforms for support and information. Neonatologists' limited involvement in creating and sharing content on social media may represent a missed opportunity to provide reliable resources to NICU families. However, confidentiality concerns, the spread of misinformation and disinformation, potential legal implications, and time constraints are legitimate and warrant consideration at both the institutional and professional levels. Addressing these concerns is essential to improve social media integration into practice. Further research is needed to explore the impact of social media on NICU care and to enhance its role in improving quality, safety, and patient satisfaction.

Data Availability Statement

The data set used in the current study is available on request from the corresponding author.

Disclaimers

The views expressed herein are those of the author(s) and do not reflect the official policy or position of the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force, the Department of the Navy, or the Department of Defense, or the U.S. Government.

Supplementary Materials

All the supplementary materials are available online on the website of www.newbornjournal.org.

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References

1. Chou WY, Hunt YM, Beckjord EB, et al. Social media use in the United States: implications for health communication. J Med Internet Res 2009;11(4):e48. DOI: 10.2196/jmir.1249.
2. Weingart SD, Faust JS. Future evolution of traditional journals and social media medical education. Emerg Med Australas 2014;26:62–66. DOI: 10.1111/1742-6723.12192.
3. Ventola CL. Social media and health care professionals: Benefits, risks, and best practices. P T 2014;39(7):491–520. PMID: 25083128.
4. George DR, Rovniak LS, Kraschnewski JL. Dangers and opportunities for social media in medicine. Clin Obstet Gynecol 2013;56(3):453–462. DOI: 10.1097/GRF.0b013e318297dc38.
5. Hameed I, Oakley CT, Ahmed A, et al. Analysis of physician use of social Media. JAMA Network Open 2021;4(7):e2118213. DOI: 10.1001/jamanetworkopen.2021.18213.
6. von Muhlen M, Ohno-Machado L. Reviewing social media use by clinicians. J Am Med Inform Assoc 2012;19(5):777–781. DOI: 10.1136/amiajnl-2012-000990.
7. Chlus N, Cassidy MRM, Monaco-Brown ML. Navigating the physician-patient relationship on social media: A comparison of current practices in adult and pediatric providers. Pediatrics 2020;146 (1_MeetingAbstract):15–16. DOI: 10.1542/peds.146.1MA1.15b.
8. Macauley R, Elster N, Fanaroff JM, et al. Ethical considerations in pediatricians' use of social media. Pediatrics 2021;147(3):e2020049685. DOI: 10.1542/peds.2020-049685.
9. Ameenuddin N. (2016). Consider using twitter to take meaningful action beyond office walls. Available from: https://publications.aap.org/aapnews/news/8514/Consider-using-Twitter-to-take-meaningful-action. [Last accessed on 18 July, 2025].
10. Cahill AM, Carlson JC. A scoping review of physician advocacy on Twitter. Cureus 2023;15(7):e41632. DOI: 10.7759/cureus.41632.
11. Bryan MA, Evans Y, Morishita C, et al. parental perceptions of the internet and social media as a source of Pediatric Health Information. Acad Pediatr 2020;20(1):31–38. DOI: 10.1016/j.acap.2019.09.009.
12. O'Keeffe GS, Clarke-Pearson K, Council on Communications and Media. The impact of social media on children, adolescents, and families. Pediatrics 2011;127(4):800–804. DOI: 10.1542/peds.2011-0054.
13. Swanson WS. (2019). Tips on using social media to educate, advocate. Available from: https://publications.aap.org/aapnews/news/14397/Tips-on-using-social-media-to-educate-advocate. [Last accessed on 18 July, 2025].
14. Krugman SD. (2021). The benefits and pitfalls of social media and pediatrics. Available from: https://publications.aap.org/journal-blogs/blog/5160/The-Benefits-and-Pitfalls-of-Social-Media-and [Last accessed on 18 July, 2025].
15. Keir A, Bamat N, Hennebry B, et al. Building a community of practice through social media using the hashtag #neoEBM. PLoS One 2021;16(5):e0252472. DOI: 10.1371/journal.pone.0252472.
16. McGowan BS, Wasko M, Vartabedian BS, et al. Understanding the factors that influence the adoption and meaningful use of social media by physicians to share medical information. J Med Internet Res 2012;14(5):e117. DOI: 10.2196/jmir.2138.
17. Horowitz E, Samnaliev M, Savich R. Seeking racial and ethnic equity among neonatologists. J Perinatol 2021;41(3):422–434. DOI: 10.1038/s41372-021-00915-z.
18. Wojcik MH, del Rosario MC, Agrawal PB. Perspectives of United States neonatologists on genetic testing practices. Genet Med 2022;24(6):1372–1377. DOI: 10.1016/j.gim.2022.02.009.
19. Haug S, Farooqi S, Wilson CG, et al. Survey on Neonatal End-of-Life Comfort Care Guidelines Across America. J Pain Symptom Manage 2018;55(3):979–984.e2. DOI: 10.1016/j.jpainsymman.2017.10.023.
20. Jacobs AP, Subramaniam A, Tang Y, et al. Trisomy 18: A survey of opinions, attitudes, and practices of neonatologists. Am J Med Genet A 2016;170(10):2638–2643. DOI: 10.1002/ajmg.a.37807.
21. Bhuiyan MN, Medina-Inojosa JR, Croghan IT, et al. Internal medicine physicians and social media: knowledge, skills, and attitudes. J Prim Care Community Health 2020;11:2150132720969022. DOI: 10.1177/2150132720969022.
22. Brown J, Ryan C, Harris A. How doctors view and use social media: A national survey. J Med Internet Res 2014;16(12):e267. DOI: 10.2196/jmir.3589.
23. Van Ravenswaay L, Parnes A, Nisly SA. Clicks for credit: An analysis of healthcare professionals' social media use and potential for continuing professional development activities. Med Educ Online 2024;29(1):2316489. DOI: 10.1080/10872981.2024.2316489.
24. Rukavina TV, Viskić J, Poplašen LM, et al. Dangers and benefits of social media on e-professionalism of health care professionals: Scoping review. J Med Internet Res 2021;23(11):e25770. DOI: 10.2196/25770.
25. Proaño A, Keir A, Campbell DM, et al. #neoTwitter: Evaluation of its use within the neonatal-perinatal community. J Perinatol 2022;42(10):1409–1411. DOI: 10.1038/s41372-022-01373-x.
26. Keir A, Bamat N, Patel RM, et al. Utilising social media to educate and inform healthcare professionals, policy-makers and the broader community in evidence-based healthcare. BMJ Evid Based Med 2019;24(3):87–89. DOI: 10.1136/bmjebm-2018-111016.
27. Dzubaty DR. Supporting neonatal intensive care unit parents through social media. J Perinat Neonatal Nur 2016;30(3): 214–217. DOI: 10.1097/JPN.0000000000000199.
28. Suarez-Lledo V, Alvarez-Galvez J. Prevalence of health misinformation on social media: Systematic review. J Med Internet Res 2021;23(1):e17187. DOI: 10.2196/17187.
29. Wolynn T, Hermann C, Hoffman BL. Social media and vaccine hesitancy: Help us move the needle. Pediatr Clin N Am 2023;70(2):329–341. DOI: 10.1016/j.pcl.2022.11.010.
30. Kline S, Reed AM, McCarty L, et al. Two steps forward, one step back: The complexity of accurately defining and measuring clinical activity in academic pediatrics. J Pediatr 2023;113446. DOI: 10.1016/j.jpeds.2023.113446.
31. Bishop CE, Machut KZ, Dammann CEL, et al. Academic neonatologist—A species at the brink of extinction? J Perinatol 2023;43(12):1526–1529. DOI: 10.1038/s41372-023-01803-4.
32. Kim HN, Wyatt TH, Li X, et al. Use of social media by fathers of premature infants. J Perinat Neonatal Nurs 2016;30(4):359–366. DOI: 10.1097/JPN.0000000000000214.
33. Taylor K, Havinga J, Moore B, et al. Social media as a source of medical information for parents of premature infants: A content analysis of prematurity-related Facebook groups. Am J Perinatol 2021;40(15):1629–1637. DOI: 10.1055/s-0041-1736539.
34. Frey E, Bonfiglioli C, Brunner M, et al. Parents' use of social media as a health information source for their children: A scoping review. Acad Pediatr 2022;22(4):526–539. DOI: 10.1016/j.acap.2021.12.006.

ORIGINAL RESEARCH

Does Routine Intensive Care Provision at 22–23 Weeks' Gestation Improve Outcomes of Infants Born between 24 and 27 Weeks?

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Abstract

Background: With the development of neonatal care, the number of weeks of gestational age at which intensive care is provided has decreased significantly, and there is much debate as to whether or not aggressive resuscitation should be performed in these extremely preterm infants. In this study, we examined whether there are differences in outcomes for extremely preterm infants between neonatal units in two countries (Australia and Japan) with differing neonatal care practices, especially in terms of resuscitation at 22–23 weeks of gestation.

Materials and methods: This was a retrospective observational study conducted in two level III NICUs [Monash Children's Hospital (MCH) in Australia and Saitama Medical Center (SMC) in Japan]. Preterm infants born between 24 and 27 weeks of gestation between 2017 and 2021 were included, and neonatal outcomes to discharge were compared.

Results: Four hundred fifty-seven (308 in MCH, 149 in SMC) infants were included. Median (IQR) birth weight was 804 (648, 975) gm for MCH vs 810 (638, 964) gm for SMC infants. Neonatal morbidities compared (MCH vs SMC) included chronic lung disease (CLD) (70.9% vs 57.5%, $p = 0.005$), necrotizing enterocolitis (5.8% vs 0.0%, $p = 0.003$), early onset sepsis (2.6% vs 0.0%, $p = 0.048$), severe interventricular hemorrhage (10.7% vs 3.4%, $p = 0.008$), periventricular leukomalacia (4.9% vs 0.0%, $p = 0.007$), retinopathy of prematurity (ROP) (9.7% vs 30.1%, $p < 0.001$), and mortality (9.4% vs 2.7%, $p = 0.009$).

Conclusion: Most neonatal morbidities were less common in extremely preterm infants born at SMC, who routinely provide intensive care to infants born at 22 weeks' gestation. Care of preterm infants at extremes of gestation (22 and 23 weeks) may have an impact on outcomes of extremely preterm infants born later in gestation.

Keywords: Brain, Gut, Heart, Infant, Lung, Neonate.

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Introduction

Preterm babies are born at less than 37 weeks' gestation, with those born at less than 32 weeks' gestation called very preterm infants and those born at 28 weeks' gestation or less identified as extremely preterm infants. With the development of neonatal care, the number of weeks of gestation at which neonatal intensive care is offered has significantly reduced, and the survival rates of very preterm infants have improved and continue to improve. For example, Edward et al.[1] reported that the survival rate for preterm infants born between 22 and 28 weeks of gestation increased from 76% in 2008–2012 to 78.3% in 2013–2016.

On the other hand, it is known that the shorter the weeks of gestation, the higher the immaturity of the premature infant, which can lead to various neonatal and long-term complications. In preterm infants, the lungs are not yet developed at birth, resulting in respiratory distress syndrome (RDS) due to a lack of surfactant. In addition, chronic lung disease (CLD) of prematurity or bronchopulmonary dysplasia (BPD) results from damage caused by mechanical ventilation, maternal infection, and inflammatory processes. Intracranial hemorrhage [intraventricular hemorrhage, (IVH)], caused by fragile intracranial blood vessels, and periventricular leukomalacia (PVL), caused by vascular immaturity, are other complications that can occur at high rates in extremely preterm infants. Other known complications include patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), infection, abnormal blood glucose control, transient hypothyroidism, anemia, metabolic bone disease, and retinopathy of prematurity (ROP). Some of these complications are transient, while others are not, and often lead to long-term impacts like visual impairment, hearing impairment, cognitive and executive brain dysfunction, cerebral palsy, learning disabilities, infection, asthma, and chronic pulmonary insufficiency,

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which require regular follow-up even after discharge from the NICU. Furthermore, they are susceptible to metabolic syndrome even into adulthood.[2–4]

There is much debate as to whether or not extremely preterm infants should be aggressively resuscitated, given their risk of long-term complications. Most national guidelines set a lower limit of weeks of gestation, and resuscitation of infants at these weeks should be decided after discussion with the family, taking into account various factors. Wilkinson et al.[5] reported that the grey zone is 23–24 weeks in the United Kingdom, 22–23 weeks in Sweden, and 24–26 weeks in the Netherlands. According to the guidelines in the State of Victoria, Australia, infants born at 22–23 weeks' gestation lie in the grey zone (zone of parental discretion—where parents' wishes are respected in terms of goals of care for the infant). With 23 weeks is the zone of active management is recommended, but parental views are respected, and 22 weeks is in the zone of palliative care recommended, but again, parental views are respected.[6] On the other hand, in Japan, for more than 20 years, babies born after 22 weeks and 0 days of gestation have been considered eligible for resuscitation, and active resuscitation has been performed upon family request.[7]

In this study, we investigated whether neonatal outcomes differ between neonatal units in two countries—Australia and Japan—that employ distinct resuscitation and care practices for infants born at the limits of viability, specifically under 24 weeks' gestation. In Japan, it is standard practice to provide intensive care to all infants born at 22–23 weeks' gestation. In contrast, Australia adopts a more selective approach, offering intensive care to infants in this gestational range only after thorough discussions with the family, considering both medical prognosis and parental preferences. To ensure comparability, we focused our analysis on infants born between 24 and 27 weeks of gestation, a range in which neonatal intensive care is routinely administered in both countries. This allowed us to assess outcomes within a more standardized framework of care while still reflecting differences in broader neonatal practices.

Materials and Methods

Study Design

This retrospective, observational study was conducted at two Level III NICUs (Monash Children's Hospital (MCH) in Australia and Saitama Medical Center (SMC) in Japan) with infants born at less than 28 weeks' gestation between January 2017 and December 2021. Patients were excluded if they had major chromosomal abnormalities or major congenital malformations.

Data Collection

Patient data from all infants born between 24 and 27 weeks' gestation were extracted from the neonatal database of each center. The NICU at SMC submits data to the Neonatal Research Network of Japan (NRNJ) while MCH is part of the Australia and New Zealand Neonatal Network (ANZNN). Local anonymized datasets from each center were extracted. The study received ethical approval from each of the institutions, and informed consent was substituted by opt-out. (Monash HREC Reg No RES-23-0000-188Q and Saitama Reg No. 2023-006). Variable definitions for the NRNJ and ANZNN are available from data dictionaries available online (https://plaza.umin.ac.jp/nrndata/indexe.htm and https://www.anznn.net, respectively).

We only included in the analysis data items that were routinely collected by both units. Furthermore, where there were differences in data definitions (e.g., while ANZNN records the side of greatest IVH grade, the NRNJ does not record the laterality, but the highest overall IVH rate), we harmonized the data fields for both maternal and infant clinical variables to facilitate analysis. Maternal factors collected included: Age, gravidity/parity, spontaneous pregnancy/infertility, complications, hypertensive disorders of pregnancy (HDP), antenatal steroids, mode of delivery, in/out born, multiple birth. Infant factors collected included: Gestational age, sex, birth body weight, Apgar Score (at 1 and 5 mins), delayed cord clamping, cord milking, intubation at birth, base excess of first neonatal blood gas, RDS, pneumothorax needed treatment, pulmonary hemorrhage, steroids for BPD (dexamethasone, hydrocortisone), length of invasive ventilation, CLD (respiratory support or oxygen need at 36 weeks PMA), early-/late-onset sepsis, treatment for ductus arteriosus, intestinal perforation, NEC (Bell stage $\geq$ 2), treatment for ROP, home oxygen therapy, IVH, PVL, hydrocephalus, and the length of admission.

Outcomes

The primary outcome was survival at discharge without major neonatal complications [severe IVH ($\geq$grade III), cystic PVL, any grade CLD (BPD), NEC ($\geq$ stage II)], ROP needing treatment. Individual morbidities were also reported.

Statistical Analysis

Statistical analysis was performed using Stata v15 (Stata Corp, College Station, TX). Shapiro-Wilk tests of normality were conducted for continuous data and results were expressed as mean (SD) or median (IQR) as appropriate. The statistical superiority of the comparison between the two units was determined using the χ^2 test or Fisher's exact test. The level of statistical significance for all analyses was set at $p = 0.05$ using two-tailed comparisons.

Results

A total of 457 infants (308 at MCH and 149 at SMC) were included in this study period, and aggressive resuscitation and NICU care were provided in all cases. Mean (SD) gestation was 25.7 (1.1) weeks for MCH vs 25.5 (1.1) weeks for SMC, and the median (IQR) birth weight was 804 grams (648, 975 grams) for MCH vs 810 grams (638, 964 grams) for SMC. The number of deaths was 29 (9.4%) in the MCH group and 4 (2.7%) in the SMC group. The number of uncomplicated survivors (without major neonatal morbidities at discharge) was 72 (23.4%) in the MCH group and 50 (33.8%) in the SMC group. The Kaplan-Meier curves of survival are also shown in Figure 1. SMC cases had a longer time to death, whereas in MCH, about half of the deaths occurred in the early postnatal period, with most deaths by day 100.

Maternal and neonatal characteristics are shown in Table 1. Maternal age was significantly older in SMC (33.4 $\pm$ 5.0 years in SMC vs 31.4 $\pm$ 5.7 years in MCH). Antenatal steroid administration was less common in the SMC group, with 67.7% of SMC vs 92.2% of MCH, and a lower percentage of SMC cases were able to receive them for the entire course. There was also no significant difference between the two groups with regard to whether the birth was in-hospital or not.

Results for neonatal complications are shown in Table 2. For the primary composite outcome, the morbidity of major complications (CLD, NEC, IVH > grade III, PVL) was 97 (66.0%) for SMC vs 235 (76.3%)

for MCH, $p = 0.021$. The survival rate without major complications was 50 (33.8%) for SMC and 72 (23.4%) for MCH, $p = 0.019$.

For primary outcomes, the survival rate was significantly higher in SMC at 97.3% vs 90.6% for MCH. CLD was more common in MCH (70.9% MCH vs 57.5% SMC), NEC was 0.0% SMC vs 5.8% MCH, IVH was 23.8% SMC vs 44.1% MCH, PVL was 0.0% SMC vs 4.9% MCH, and ROP requiring treatment was 30.1% SMC vs 9.7% MCH.

There was a clear difference in the number of cases requiring tracheal intubation at birth, 97.3% in SMC vs 34.7% in MCH. The percentage of cases requiring surfactant was similar between the two groups. There was a significant difference in the number of days required for extubation (32 days for SMC vs 15 days for MCH). The percentage of cases requiring home oxygen therapy was 14.7% for SMC and 20.8% for MCH, with no significant difference. Patent ductus arteriosus requiring treatment was 33.1% SMC vs 40.3% MCH, with no significant difference. The duration required for discharge from the hospital was significantly shorter in MCH (102 days) than in SMC (121 days).

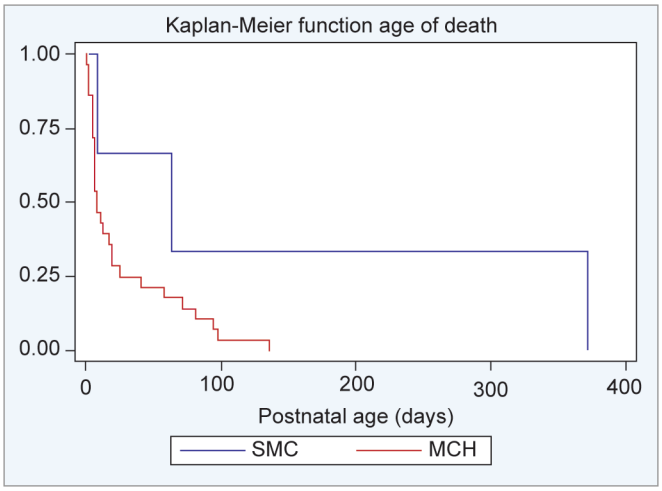

Fig. 1: Kaplan-Meier plot for time of death

Discussion

The current study compared survival rates and the frequency of each complication in extremely preterm infants born between 24 and 27 weeks of gestation at two level III NICU facilities in Australia and Japan. The uncomplicated survival rate was significantly higher at SMC, and most neonatal complications were lower at SMC.

Differences in health professionals' attitudes toward resuscitation and intensive care at 22–23 weeks' gestation significantly influence clinical decision-making and outcomes. In Japan, a strong cultural and institutional commitment to providing active treatment at these gestational ages reflects a collective belief in the potential for survival and long-term benefit, leading to routine resuscitation and intensive care. Conversely, in Australia, care decisions are more individualized, shaped by a cautious approach that weighs prognosis, quality of life, and parental preferences. These contrasting attitudes underscore how professional values and national norms can shape thresholds for viability and the intensity of neonatal care. We acknowledge that variations in clinical approaches and cultural or ethnic backgrounds may influence neonatal outcomes even within the 24–27 weeks gestational range. However, rather than viewing these differences as limitations, we argue they enrich the broader conversation around neonatal care. By examining and understanding each other's practices, there is an opportunity for mutual learning and refinement of care strategies, ultimately aiming to improve outcomes for extremely preterm infants across diverse healthcare settings.

First, we compare birth status. Among the items under consideration in this study, the 5-minute Apgar score and base excess value are relevant. In particular, the base excess value reflects the condition of the infant immediately after birth and is considered to be influenced by obstetric management and delivery status. This is still a convincing result that SMC, which is accustomed to handling more preterm infants, did better. On the other hand, the Apgar score is given at 5 minutes after birth, and is influenced by neonatal resuscitation techniques as well as the general condition of the infant at the time of birth. It is also important to note that

Table 1: Maternal and neonatal characteristics

Characteristic	*SMC*	*MCH*	*p-value*
Maternal age (years)	33.4 ± 5.0	31.4 ± 5.7	<0.001
Hypertensive disorder of pregnancy	18 (12.1%)	45 (14.6%)	0.46
Antenatal steroids (total)	101 (67.7%)	284 (92.2%)	<0.001
Incomplete	22 (14.8%)	74 (24.3%)	
Complete	79 (53.0%)	210 (68.9%)	
Plurality			
Singleton	123 (82.6%)	233 (75.6%)	0.056
Twin	26 (17.4%)	66 (21.4%)	
Triplet	0 (0.0%)	9 (2.9%)	
Male sex	72 (48.3%)	152 (49.4%)	0.84
Birth body weight (gm) (Fenton)	810 (638, 964) 0.049 (−0.838, 0.741)	804.5 (648, 975) −0.014 (−0.693, 0.472)	0.46 0.55
Gestational age (weeks)	25.5 (1.1)	25.7 (1.1)	0.26
Inborn	143 (96.0%)	284 (92.2%)	0.13
Apgar score (5 min)	7 (5, 8)	7.5 (6, 8)	<0.001
Base excess	−2.8 (−5.4, −0.2)	−5 (−8, −2)	<0.01

Data expressed as mean (SD), median (IQR), or *n* (%)

Table 2: Neonatal complications

Neonatal events	*SMC (n = 149)*	*MCH (n = 308)*	*p-value*
Intubation at birth	145 (97.3%)	107 (34.7%)	<0.001
Day of last extubation	32 (15.47)	15 (3.33)	<0.01
Needed surfactant	122 (81.9%)	248 (80.5%)	0.73
Pneumothorax	9 (6.1%)	19 (6.2%)	0.97
Chronic lung disease	84 (57.5%)	205 (70.9%)	0.005
Home oxygen	21 (14.7%)	64 (20.8%)	0.12
PDA needed treatment	49 (33.1%)	124 (40.3%)	0.14
Necrotizing enterocolitis	0 (0.0%)	18 (5.8%)	0.003
Intestinal perforation	7 (4.7%)	11 (3.6%)	0.55
Early onset sepsis (<48 hrs)	0 (0.0%)	8 (2.6%)	0.048
IVH	34 (23.8%)	136 (44.1%)	<0.01
Grade I	12 (8.1%)	71 (23.3%)	
Grade II	17 (11.4%)	35 (11.5%)	
Grade III	2 (1.3%)	5 (1.6%)	
Grade IV	3 (2.0%)	25 (8.2%)	
PVL	0 (0.0%)	13 (4.9%)	0.007
ROP (needed treatment)	44 (30.1%)	30 (9.7%)	<0.001
Death	4 (2.7%)	29 (9.4%)	0.009
Length of stay (days)	121 (102, 152)	102 (82, 129)	<0.001
Major morbidities	97 (66.0%)	235 (76.3%)	0.021
Survival without major morbidities	50 (33.8%)	72 (23.4%)	0.019

Data expressed as mean (SD), median (IQR), or *n* (%)

some items may differ depending on the person who gives the score. Therefore, further study is needed to interpret the significant differences observed in this study.

Next, complications affected by postnatal management are discussed. There are many differences in the way preterm infants are managed at each facility, which may impact the results of this study. Therefore, we will discuss each item in turn. The differences in the management of preterm infants at the two facilities are shown in Table 3. In particular, there are distinctive differences in fluid volume strategies in the early postnatal period, sedation during intubation, and infection prevention. We will discuss the relationship between these differences in management and the results of this study.

In this study, the incidence of CLD was lower in SMC, but the duration of intubation, which is generally considered to be related to CLD, was significantly longer in SMC. The NIPPV device used at SMC can only use Biphasic and CPAP modes and cannot use IMV mode. We believe this is one of the reasons for the long duration of intubation at SMC.

One of the differences in management practices that may have caused the difference in CLD incidence is the setting of fluid intake. As shown in the Table 3, MCH generally administered more fluids than SMC. Starr et al.[8] noted an association between early postnatal fluid balance and short- and long-term respiratory function, which is consistent with the present results. Another major difference in respiratory management is the use of sedatives. In MCH, sedatives and muscle relaxants were used only if necessary during ventilatory management, whereas in SMC, respiratory management is based on spontaneous breathing, and sedatives are rarely used for respiratory management purposes. However, the RCT reported by Sudo et al.[9] in 2023 showed no significant association between the use of fentanyl during intubation and CLD, and the present results may suggest that the level of sedation is not very relevant in CLD. We believe that further study is needed on these issues. Considering that the definition of CLD is the presence or absence of respiratory support at the modified 36-week period, it is possible that the degree of respiratory impairment at the time of discharge from the hospital is not so different between the two centers.

In the present study, grade 1 IVH was more common in MCH than SMC. We believe that this is undeniably related to the use of high-performance ultrasound probes in MCH, since the assessment of the severity of IVH is done by ultrasound examination. PVL and severe IVH were also significantly more common in MCH. The major difference between SMC and MCH in circulatory management is whether or not echocardiography is performed by neonatologists. Circulation is known to influence the incidence of IVH, PVL, symptomatic PDA, and intestinal perforation, and Regan et al.[10] also reported that early hemodynamic screening in preterm infants can influence their outcome. However, the possibility of invasiveness of performing the echocardiography has been addressed in early screening, and we believe that familiarity with echocardiography in younger gestational age infants may be an advantage. As for the difference in the incidence of severe IVH, neonatologists can perform head ultrasound, which allows them to detect IVH at an early stage and begin supportive treatment, such as sedation, possibly reducing the severity of the condition.

In this study, there was no significant difference in SIP between the two centers, but NEC was significantly higher at MCH. NEC

Table 3: The management of preterm infants at each facility

Theme		*SMC*	*MCH*
Resuscitation	Cord blood	Cord milking (single method)	Delayed cord clamping
	Respiratory assistance	Jackson Rees	T-piece
Respiration	Ventilation mode	SIMV/HFO/volume guaranteed	SIMV/HFO/volume guaranteed
	NIPPV	CPAP/HFNC/LFNC	S/T mode/CPAP/HFNC/LFNC
	Surfactant (type, method, and target of administration)	Surfactant (120 mg/kg) via TT, In case of $FiO_2 > 0.4$	Poractant Alfa (200 mg/kg) via ETT, depends on condition
	Prevention of BPD	Inhaled steroid, diuretics	Early extubation
	Steroids for BPD	Hydrocortisone (2 mg/kg/day for 3 days, 1 mg/kg/day for 3 days, 0.5 mg/kg/day for 3 days) If insufficient, dexamethasone (DART protocol)	Dexamethasone (DART protocol)
	Timing of extubation	Careful not to reintubate	At the earliest time possible
Circulation	Indicators	Blood pressure, fluid balance, and echocardiogram findings	Blood pressure, body weight
	Total fluid intake	Day 0 50 mL/kg/day Day 1 60 mL/kg/day Day 2 70 mL/kg/day	Day 0 60 mL/kg/day Day 1 80 mL/kg/day Day 2 100 mL/kg/day
	Treatment for PDA	Ibuprofen, indomethacin, acetaminophen	Acetaminophen
Feeding	Enteral feeding	Fortified mother's milk, artificial milk	Fortified mother's milk, artificial milk
	Parenteral feeding	Glucose, amino acid, electrolyte, Ca, P, Intralipid®	Glucose, amino acid, electrolyte, Ca, P, Mg, Zn, Se, Iodine, Copper, Acetate, SMOF lipid®
	Probiotics	Bifidobacterium breve M16-V	Bifidobacterium bifidum + *Lactobacillus acidophilus*
	Enema	Glycerin (2× dilution, 1 mL/kg/dose, three times daily)	Not used routinely
	Increase in enteral feeding	Less than 20 mL/kg/day	Less than 30 mL/kg/day
Neuroprotection	Sedation (as needed)	Phenobarbital, fentanyl	Phenobarbital, morphine
	Others	GA <28 weeks: prophylactic indomethacin	
Infection	Treatment for early-onset infection	Ampicillin + gentamicin	Benzylpenicillin + gentamicin
	Prophylactic antibiotics	GA ≦ 24 weeks: ABPC + GM + IVIG + FLCZ GA < 26 weeks: ABPC + GM + IVIG	
Treatment	Anemia of prematurity	Erythropoietin, iron	Iron
	Bone metabolism	Vit D3, calcium, phosphorus as needed	Vit D3 + calcium
	ROP	Laser	Laser, anti-VEGF agents

ABPC, ampicillin; Ca, calcium; CPAP, continuous positive airway pressure; FLCZ, fluconazole; GM, gentamicin; HFNC, high-flow nasal cannula; HFOV, high-frequency oscillatory ventilation; IVIG, intravenous immunoglobulin; LFNC, low-flow nasal cannula; Mg, magnesium; NIPPV, noninvasive positive pressure ventilation; P, phosphate; PCG, Benzylpenicillin; ROP, retinopathy of prematurity; Se, selenium; SIMV, synchronized intermittent mandatory ventilation; S/T mode, spontaneous/timed mode; Zn, zinc

is thought to develop as a result of intestinal mucosal damage triggered by impaired blood flow and other factors against a background of disrupted intestinal flora due to compromised gastrointestinal tract and immunocompetence in preterm infants. This may be related to differences in methods of circulatory control and infection prevention between the two centers.

The methods of infection prevention in the early postnatal period are different. SMC routinely administers immunoglobulin to infants with GA <26 weeks and IgG < 300 mg/dL at birth, which is consistent with the conclusion of the 2020 Cochrane study that IVIG reduces sepsis by 3%.[11]

As for ROP, more cases in SMC required laser therapy, while Shah et al.[12] reported that 3–4 times more cases required treatment in Japan than in other countries. One cause to consider is the difference in oxygen use: SMC does not aggressively use steroids for CLD because of concerns about the long-term poor neurological prognosis caused by steroids. This may lead to exposure to high oxygen concentrations and prolonged oxygen use, which may lead to worsening ROP.

The duration of hospitalization was significantly longer in SMC. This may be related to the fact that families in the SMC program start guiding the care of their children later than those in the MCH

program. This may be a problem that should be improved in the future to avoid unnecessary separation of mother and child as much as possible.

As described above, we have examined the differences in treatment and management methods that may cause the development of each complication. The development of complications is not only related to therapeutic management, but also to daily nursing care and environmental influences. We believe that it is undeniable that SMC with experience in the care of extremely preterm infants at the threshold of viability may have had a better survival rate for all preterm infants.

Conclusion

In this study, we found that SMC had relatively fewer major neonatal complications and a better survival rate without major morbidity in extremely preterm infants born between 24- and 27-weeks' gestation. There are some differences in management practices between the two centers, and we believe that each has its advantages. However, we believe that taking care of extremely preterm infants increases the likelihood of a better prognosis for all infants.

Author Contributions

Conceptualization: YM, FN, KT, and AM; methodology: YM and AM; data acquisition: YM and KT; interpretation of data: YM and AM. All authors read and approved the final manuscript.

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References

1. Bell E, Hintz R, Hansen N, et al. Mortality, in-hospital morbidity, care practices, and 2-year outcomes for extremely preterm infants in the US, 2013-2018. JAMA 2022; 327(3):248–263. DOI: 10.1001/jama.2021.23580.
2. Hovi P, Andersson S, Eriksson J, et al. Glucose regulation in young adults with very low birth weight. N Engl J Med 2007;356:2053–2063. DOI: 10.1056/NEJMoa067187.
3. Kajantie E, Osmond C, Barker DJ, et al. Preterm birth—a risk factor for type 2 diabetes? The Helsinki birth cohort study. Diabetes Care 2010;33:2623–2625. DOI: 10.2337/dc10-0912.
4. Crump C, Winkleby MA, Sundquist K, et al. Risk of hypertension among young adults who were born preterm: A Swedish national study of 636,000 births. Am J Epidemiol 2011;173:797–803. DOI: 10.1093/aje/kwq440.
5. Wilkinson D, Verhagen E, Johansson S, et al. Thresholds for resuscitation of extremely preterm infants in the UK, Sweden, and Netherlands. Pediatrics 2018;142(Suppl 1):S574–S584. DOI: 10.1542/peds.2018-0478I.
6. Safer Care Victoria. Extreme Prematurity Guideline: Clinical Guidance. Available from: https://www.safercare.vic.gov.au/best-practice-improvement/clinical-guidance/neonatal/extreme-prematurity [Last accessed August, 2024].
7. Isayama T. The clinical management and outcomes of extremely preterm infants in Japan: Past, present, and future. Transl Pediatr 2019;8(3):199–211. DOI: 10.21037/tp.2019.07.10.
8. Starr M, Griffin R, Gist K, et al. Association of fluid balance with short- and long-term respiratory outcomes in extremely premature neonates. JAMA Netw Open 2022;5(12):e2248826.
9. Sudo Y, Seki-Nagasawa J, Kajikawa D, et al. Effect of fentanyl for preterm infants on mechanical ventilation: A systematic review and meta-analysis. Neonatology 2023;120(3):287–294. DOI: 10.1159/000529440.
10. Giesinger R, Rios D, Chatmethakul T, et al. Impact of early hemodynamic screening on extremely preterm outcomes in a high-performance center. Am J Respir Crit Care Med 2023;208(3):290–300. DOI: 10.1164/rccm.202212-2291OC.
11. Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2020;1(1):CD000361. DOI: 10.1002/14651858.CD000361.pub4.
12. Shah P, Lui K, Sjörs G, et al. Neonatal outcomes of very low birth weight and very preterm neonates: An international comparison. J Pediatr 2016;177:144–152. DOI: 10.1016/j.jpeds.2016.04.083.

CLINICAL TECHNIQUE

Oral 10% Dextrose was More Effective than Expressed Breast Milk for Pain Relief in Neonates Receiving Their First Dose of Hepatitis B Vaccination

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Abstract

Background: Pain management is often overlooked in neonates undergoing minor procedures. Other than traditional analgesics, several non-pharmacological methods, such as expressed breast milk (EBM) and oral sweet solutions like dextrose, have been tried, but the comparative efficacy remains debated.

Objective: To compare the analgesic effects of oral 10% dextrose vs EBM in neonates before they receive their first dose of hepatitis B vaccination.

Materials and methods: A single-center prospective observational study was conducted with 300 neonates randomly assigned into two groups of 150 each. Neonates received either 2 mL of EBM or 10% dextrose 2 minutes before vaccination. Pain was assessed using the Neonatal Infant Pain Scale (NIPS), duration of crying, and heart rate.

Results: Mean NIPS score was significantly lower in the 10% dextrose group (2.1 ± 1.9) compared to the EBM group (5.3 ± 2.7; $p < 0.001$). The cry time was also significantly lower in the dextrose group (14.67 ± 4.6 s) vs the EBM group (82.24 ± 26.57; $p < 0.001$). The groups did not differ in the changes in heart rate.

Conclusion: Oral 10% dextrose was more effective than EBM in reducing procedural pain in neonates before they received their first dose of hepatitis B vaccination.

Keywords: 10% dextrose, Expressed breast milk, Neonatal pain, Neonatal Infant Pain Scale, Non-pharmacological analgesia.

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Key Points

- Pain management is often overlooked in neonates undergoing minor procedures.
- Several studies have examined the efficacy of non-pharmacological methods such as expressed breast milk (EBM) and oral sweet solutions, but the results are still debated.
- In this study, the authors compared two groups of 150 infants each who received 10% dextrose or EBM before their first dose of hepatitis B vaccination. Pain was assessed using the NIPS, duration of crying, and heart rate.
- Oral 10% dextrose was more effective than EBM in reducing procedural pain.

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Introduction

In neonates, pain is not only an unpleasant sensory/emotional experience, but it might even cause neural tissue damage.[1] Both premature and full-term infants have to undergo numerous painful procedures such as blood draws and vaccinations.[2] Many pharmacological agents, such as opioids, non-steroidal medications, and topical analgesics, are used routinely, but the safety of these agents is uncertain. Hence, several non-pharmacologic strategies have been evaluated for prevention/relief of pain, such as feeding small doses of 10–25% sucrose/dextrose applied on pacifiers or spoons, breastfeeding, non-nutritive sucking, kangaroo maternal care, limiting environmental stimuli, swaddling, or positioning with a facilitated tuck where the arms and legs are held in a flexed position. These measures, used singly or in combination, seem to be effective in late preterm and term neonates in reducing pain-associated responses.[3]

Sweet-tasting solutions such as sucrose and concentrated dextrose can prevent pain in neonates by stimulating the release of endogenous opioids and activating μ receptors.[4] However, the efficacy of repeated administration is uncertain.[5] We are particularly interested in dextrose solutions as these are readily available in hospitals. Concentrated solutions such as 25% dextrose may be effective, but concerns remain about the possibility of fluctuations in serum glucose levels, especially in preterm infants. Other sweet-tasting solutions, such as fructose, have also been evaluated but need more studies.[6]

In this quality-improvement (QI) study, we compared oral 10% dextrose (D10W) solutions for their analgesic effects with those of

EBM in newborn infants receiving their first hepatitis B vaccination.[7] We used the Neonatal Infant Pain Scale (NIPS), a behavioral–physiological assessment tool for evaluating pain; there are six indicators on a 0–7 scale: facial expression, cry, breathing patterns, arms, legs, and state of arousal: each is scored on a 0–1 scale, except "cry" which is scored 0–2. A total score >3 is accepted as indicating pain.[8] We also compared the changes in heart rate and the duration of the cry. Details are provided in the Materials and Methods section.

Materials and Methods

We conducted a prospective observational study at Jawaharlal Nehru Hospital & Research Centre in Bhilai, India, after due approval by the Institutional Review Board. All infants who visited the clinical center for their first Hepatitis B immunization were enrolled after a written, informed parental consent.[9–12] The study was conducted over 2 years.

The study included continuously evaluated, healthy, exclusively breastfed infants born at ≥37 weeks' gestation with a birth weight ≥2 kg, who were receiving their first dose of the Hepatitis B vaccine.[13] Preterm or neonates weighing <2 kg, or those with respiratory distress, congenital anomalies, neurological deficits, or requiring sedatives, were excluded. We selected 300 neonates and randomized them into a 1:1 ratio into two equal intervention groups (150 infants) from a random number table.[14] A pre-structured proforma was completed for each neonate, which included the mother's name, the infant's birth weight, gestational age, gender, and notable clinical findings.[15,16] We filled sterile droppers with approximately 2 mL (up to a marked line) of EBM or 10% dextrose (D10W) and administered one orally per randomization, 2 min before taking the infant to the immunization room for vaccination. All infants were held in the classical holding position during the injection.[17] The injection site on the anterolateral aspect of the right thigh was cleaned using an alcohol-dipped cotton swab, followed by an intramuscular administration of 0.5 mL of the vaccine. The outcome variables included the duration of cry from the time of insertion of the needle, heart rate, and the NIPS score.[8,18–20]

The severity of behavioral/physiological pain responses to procedures was classified using the NIPS score.[21,22] These scores range between 0 and 7, with three subcategories: Mild (0–2), moderate (3–4), and severe pain (5–7).

Parameter	*Finding*	*Points*
Facial expression	Relaxed	0
	Grimace	1
Cry	No cry	0
	Whimper	1
	Vigorous cry	2
Breathing patterns	Relaxed	0
	Change in breathing	1
Arms	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
Legs	Restrained	0
	Relaxed	0
	Flexed	1
	Extended	1
State of arousal	Sleeping	0
	Awake	0
	Fussy	1

The duration of cry was timed from the time of skin puncture until cessation of cry. Heart rate was recorded at 60 and 120 seconds after skin puncture.

Statistical Analysis

The subjects were randomized using the software program SPSS Statistics for Windows, version 26.0.[23] Continuous variables were presented as mean ± standard deviation (SD), and were summarized as mean ± SD. Data was checked for normality; normally distributed continuous variables were compared using the unpaired *t*-test or analysis of variance, whereas non-parametric data were analyzed using the Mann-Whitney *U* or Kruskal–Wallis tests.[24–27] Categorical variables were presented as absolute numbers and percentages, and the subgroups were compared using either the Chi-squared test or Fisher's exact test. For all data, *p*-values < 0.05 were chosen as significant.[28–30]

Results

In our cohort, the birth weight (grams) was 2828 ± 472.3 grams. Most (229, 76.3%) weighted >2.5 kgs, 71 (23.7%) weighted <2.5 kgs. One 159 (53%) were males and 141 (47%) were females. More than half (191, 63.7%) were delivered by cesarean delivery, and 109 (36.3%) were delivered by normal vaginal delivery. The clinical details of the two groups treated with D10W or EBM, and those of the entire cohort, are summarized in Table 1.

Table 2 shows the distribution of infants by NIPS assessment of the severity of pain. Out of 159 male neonates, 41.5% had mild pain, and out of 141 female neonates, 44.8% had mild pain, and the difference was not significant (*p*-value = 0.314). In our 203 neonates with a birth weight of 2–3 kg, 42.4% had mild pain and 35.5% had

Table 1: Demographics

	Pain-relieving strategy			
Parameters	*10% Dextrose*	*EBM*	*Total*	*p-value*
Gender				
Male	82 (54.7%)	77 (51.3%)	159 (53%)	0.563
Female	68 (45.3%)	73 (48.7%)	141 (47%)	
Weight (kg)				
<2.5 kgs	33 (25.3%)	38 (22%)	71 (23.7%)	0.497
>2.5 kgs	117 (74.7%)	112 (78%)	229 (76.3%)	
Total	150 (100%)	150 (100%)	300 (100%)	
Mean weight (gm)	2818.7 ± 458.3	2831 ± 450.2	2828 ± 472.3	
Mode of delivery				
NVD	54 (36%)	55 (36.7%)	109 (36.3%)	0.904
LSCS	96 (64%)	95 (63.3%)	191 (63.7%)	
Total	150 (100%)	150 (100%)	300 (100%)	

Table 2: Distribution of NIPS scores after using specific pain-relieving strategies

	Pain-relieving strategy			
Pain score	*10% dextrose*	*EBM*	*Total*	*p-value*
Mild pain	91 (60.7%)	38 (25.3%)	129 (43%)	<0.001
Moderate pain	37 (24.7%)	63 (42%)	100 (33.3%)	
Severe pain	22 (14.6%)	49 (32.7%)	71 (23.7%)	
Total	150 (100%)	150 (100%)	300 (100%)	

Table 3: Neonatal Infant Pain Scale assessment after using specific pain-relieving strategies

Pain assessment components	*Pain-relieving strategy*		*Total*	*p-value*
	10% dextrose	*EBM*		
Facial expression				
Grimace	40 (26.7%)	114 (76%)	154 (51.3%)	<0.001
Relaxed	110 (73.3%)	36 (24%)	146 (48.7%)	
Cry				
No cry	100 (66.7%)	30 (20%)	130 (43.3%)	<0.001
Vigorous cry	21 (14%)	74 (49.3%)	95 (31.7%)	
Whimper	29 (19.3%)	46 (30.7%)	75 (25%)	
Breathing patterns				
Change in breathing	48 (32%)	120 (80%)	168 (56%)	<0.001
Relaxed	102 (68%)	30 (20%)	132 (44%)	
Arms				
Flexed/extended	41 (27.3%)	116 (77.3%)	157 (52.3%)	<0.001
Relaxed/restrained	109 (72.7%)	34 (22.7%)	143 (47.7%)	
Legs				
Flexed/extended	64 (42.7%)	123 (82%)	187 (62.3%)	<0.001
Relaxed/restrained	86 (57.3%)	27 (18%)	113 (37.7%)	
State of arousal				
Fussy	58 (38.7%)	121 (80.7%)	179 (59.7%)	<0.001
Sleeping/awake	92 (61.3%)	29 (19.3%)	121 (40.3%)	
Total	150 (100%)	150 (100%)	300 (100%)	

moderate pain. In the subgroup of 95 neonates with a birth weight of 3–4 kg, 45.3% had mild pain and 28.4% had moderate pain, but this difference was not significant ($p = 0.527$).

The details of the NIPS assessment are shown in Table 3. After giving D10W, the NIPS scores were 2.1 ± 1.9, which were lower than those given by EBM (5.3 ± 2.7; $p < 0.001$). The cry time was also significantly lower in those who received D10W (14.67 ± 4.6 s) than in the EBM group (82.24 ± 26.57; $p < 0.001$). The heart rate was not different in the two groups at 60 seconds (149 ± 18.5 vs 148.4 ± 18.9, $p = 0.555$) and 120 seconds (131.6 ± 16.8 vs 132.8 ± 17.8, $p = 0.886$).

Discussion

We found D10W as more effective than EBM in pain prevention/relief in infants receiving their first dose of Hepatitis B vaccine. These findings are important because the neonatal brain is highly plastic and is developing rapidly.[31] Pain experiences during this critical period can influence the formation of neural circuits involved in pain processing and emotional regulation.[32] Even though neonates might differ from adults in their perception of pain, they clearly demonstrate physiological and emotional responses to painful stimuli. These responses can include crying, facial grimacing, and changes in body posture. Research suggests that neonates can form implicit memories of painful experiences, which may influence their future pain responses and emotional development. This underscores the importance of minimizing painful procedures and providing adequate pain relief when necessary.[33] Repeated or prolonged exposure to pain during the neonatal period can alter the normal trajectory of brain development, both in terms of its structure and function.[34,35] Neonatal pain experiences have been associated with altered pain sensitivity later in life, as well as potential impacts on cognitive function, attention, and behavior. These effects can persist into childhood and even adolescence.[36] Under-treated painful stimuli in newborns can lead to long-term changes in the stress response system, potentially affecting how individuals cope with stress and regulate emotions throughout their lives.[37]

This study demonstrates that D10W is more effective than EBM in reducing pain and cry duration during hepatitis B vaccination in neonates, as evidenced by lower NIPS scores and shorter cry times. Our findings are similar to those of Shanthi et al.,[38] who compared 10% dextrose with EBM for relief in procedural pain in an RCT in newborn infants. They used a revised premature infant pain profile (PIPP) score (PIPP-R; range 0–21, including contextual (gestational age, behavioral state), physiological (change in heart rate, change in SpO_2), and facial indicators (brow bulge, eye squeeze, nasolabial furrow).[39] Each of these was scored 0–3; PIPP-R < 6 was classified as minimal, 7–12 as moderate, and >12 as severe pain. In this study, the PIPP-R (mean ± standard deviation) was 7.19 ± 2 at initiation, 5.5 ± 1.5 at 30 seconds, and 4.28 ± 1.65 at 60 seconds. In comparison, infants treated with 10% dextrose solution had a significantly lower PIPP-R of 4.97 ± 1.42 at initiation, 2.36 ± 1.44 at 30 seconds, and 1.69 ± 1.53 at 60 seconds ($p < 0.05$).

In contrast to our findings, Dasari et al.[40] found EBM to be more efficacious than D10W in reducing procedural pain in their double-blinded RCT. They compared 30 infants in the 10% dextrose group and 30 receiving EBM, using the NIPS scale. Infants in the EBM group showed a NIPS score of 4 ± 0.7 at 30 seconds, which was significantly lower than 6 ± 1.2 in the 10% dextrose group, which was statistically significant. The duration of cry in the EBM group (44.53 ± 28.63 seconds) was lower than that of the 10% dextrose group (52.46 ± 43.58), which was not significantly different. Subgroup analysis showed a significant difference between NIPS scores ($p < 0.001$) across the timelines in each group. There was a significant change in heart rate across the timelines in each group ($p < 0.001$). They concluded that both D10W and EBM are efficacious in reducing pain in neonates, but there was no need to choose one over the other.

Similar to our results that D10W is efficacious in pain relief, 25% dextrose has also been shown to be beneficial. We were less enthusiastic about 25% dextrose because of the fear of altering blood glucose levels, and also because we do not routinely store 25% dextrose in our neonatal unit. Jha et al.[41] showed that 25% dextrose reduced pain as compared to EBM/sterile water. They compared the groups in a randomized placebo-controlled study using the PIPP score: infants treated with 25% dextrose group showed significantly lower scores than those who received EBM or sterile water (2.94 ± 1.41 vs 7.42 ± 1.69 and 10.56 ± 1.69; $p < 0.001$). The maximal heart rate was also significantly lower in the 25% dextrose group, but no difference was found between the EBM and sterile water groups ($p = 0.23$). SpO_2 was significantly higher in the 25% dextrose group, but for only the initial 2.5 minutes. Cry times were significantly lower in the intervention groups. There was no difference in outcomes in term vs preterm infants. They concluded that the use of the 2 mL 25% dextrose group was more effective in reducing procedural pain from venipuncture compared to the 5 mL EBM. The return of physiological markers (maximal heart rate and SpO_2) to baseline was faster and more complete in the 25% dextrose group. The lack of significant heart rate differences suggests that

both interventions similarly stabilize physiological responses.[42] The behavioral indicators in the NIPS scale provided robust evidence of the adequacy of D10W for activation of the endogenous opioid system.[2] Others have reported similar results, and there is some support from a systematic review and meta-analysis.[43–46] The Cochrane neonatal group has focused on using dextrose gel for the management of hypoglycemia, but their research does not suggest that it is potentially useful for pain management.[46] Hence, there is a need for more studies.

Conclusion

Our data show that oral 10% dextrose was more effective than EBM in reducing procedural pain in neonates before they received their first dose of hepatitis B vaccination. D10W-treated infants showed a relaxed facial expression, shorter cry, better breathing patterns, and a relaxed posture. Most were sleeping or awake. Our study does have limitations, such as its focus on term neonates and the single-center design, but we are still comfortable in stating that oral D10W deserves further study for its analgesic effects following painful procedures.

References

1. Zeltzer LK, Anderson CT, Schechter NL. Pediatric pain: Current status and new directions. Curr Probl Pediatr 1990;20(8):409–486. Available from: https://pubmed.ncbi.nlm.nih.gov/2209068/.
2. Witt N, Coynor S, Edwards C, et al. A guide to pain assessment and management in the neonate. Curr Emerg Hosp Med Rep 2016;4:1–10. DOI: 10.1007/s40138-016-0089-y.
3. Anand KJ, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl J Med 1987;317(21):1321–1329. DOI: 10.1056/NEJM198711193172105.
4. Barr RG, Pantel MS, Young SN, et al. The response of crying newborns to sucrose: Is it a "sweetness" effect? Physiol Behav 1999;66(3):409–417. DOI: 10.1016/s0031-9384(98)00294-7.
5. Stevens B, Yamada J, Ohlsson A, et al. Sucrose for analgesia in newborn infants undergoing painful procedures. Cochrane Database Syst Rev 2016;7(7):CD001069. DOI: 10.1002/14651858.CD001069.pub5.
6. Akçam M. Oral fructose solution as an analgesic in the newborn: A randomized, placebo-controlled and masked study. Pediatr Int 2004;46(4):459–462. DOI: 10.1111/j.1442-200x.2004.01932.x.
7. Pearlman SA. Advancements in neonatology through quality improvement. J Perinatol 2022;42(10):1277–1282. DOI: 10.1038/s41372-022-01383-9.
8. Gallo AM. The fifth vital sign: Implementation of the Neonatal Infant Pain Scale. J Obstet Gynecol Neonatal Nurs 2003;32(2):199–206. DOI: 10.1177/0884217503251745.
9. Berger ML, Dreyer N, Anderson F, et al. Prospective observational studies to assess comparative effectiveness: The ISPOR good research practices task force report. Value Health 2012;15(2):217–230. DOI: 10.1016/j.jval.2011.12.010.
10. JLN-Hospital. J.L.N. Main Hospital and Research Centre. Bhilai: J.L.N. Main Hospital and Research Centre; 2025. Available from: https://accr.natboard.edu.in/online_user/hospital_profile.php?token=nay(2fbOM@UtPeqAizLF)C1vjI7VJh1cmx0G6E4Hk31rKW1g07T15BZd$w8g1C7YGJOmZ42xazK.
11. Parija PP, Mohan Kumar M. Hepatitis B vaccine birth dose in India: Time to reconsider. Hum Vaccin Immunother 2020;16(1):158–160. DOI: 10.1080/21645515.2019.1640557.
12. Manti S, Licari A. How to obtain informed consent for research. Breathe (Sheff) 2018;14(2):145–152. DOI: 10.1183/20734735.001918.
13. Pattyn J, Hendrickx G, Vorsters A, et al. Hepatitis B Vaccines. J Infect Dis 2021;224(12 Suppl 2):S343–S351. DOI: 10.1093/infdis/jiaa668.
14. Zabor EC, Kaizer AM, Hobbs BP. Randomized controlled trials. Chest 2020;158(1S):S79–S87. DOI: 10.1016/j.chest.2020.03.013.
15. Editors P-M. An unbiased scientific record should be everyone's agenda. PLoS Med 2009;6(2):e1000038. DOI: 10.1371/journal.pmed.1000038.
16. Acharya S, Koul P, Sharma K. Impact of non-pharmacological pain management technique on physiological parameters and duration of cry among neonates while undergoing heel prick. Int J Community Med Public Health 2025;12(6):2533–2537. DOI: 10.18203/2394-6040.ijcmph20251444.
17. Yin HC, Cheng SW, Yang CY, et al. Comparative survey of holding positions for reducing vaccination pain in young infants. Pain Res Manag 2017;2017:3273171. DOI: 10.1155/2017/3273171.
18. Bhowmick R, Bharti B, Kumar P, et al. Anterolateral thigh measurements by ultrasound in neonates and young infants to ensure safe intramuscular injections during vaccination in low- and middle-income countries. J Trop Pediatr 2020;66(2):114–120. DOI: 10.1093/tropej/fmz039.
19. Dulong C, Brett K, Argáez C. Skin preparation for injections: A review of clinical effectiveness, cost-effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562932/.
20. Velu V, Nandakumar S, Shanmugam S, et al. Comparative efficacy of two dosages of recombinant hepatitis B vaccine in healthy adolescents in India. Pediatr Infect Dis J 2007;26(11):1038–1041. DOI: 10.1097/INF.0b013e3181342887.
21. Lawrence J, Alcock D, McGrath P, et al. The development of a tool to assess neonatal pain. Neonatal Netw 1993;12(6):59–66. PMID: 8413140.
22. Sarkaria E, Gruszfeld D. Assessing neonatal pain with NIPS and COMFORT-B: Evaluation of NICU's staff competences. Pain Res Manag 2022;2022:8545372. DOI: 10.1155/2022/8545372.
23. Shahrul AI, Syed Mohamed AMF. A comparative evaluation of statistical product and service solutions (SPSS) and ChatGPT-4 in statistical analyses. Cureus 2024;16(10):e72581. DOI: 10.7759/cureus.72581.
24. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: A guide for non-statisticians. Int J Endocrinol Metab 2012;10(2):486–489. DOI: 10.5812/ijem.3505.
25. Andrade C. A student's guide to the classification and operationalization of variables in the conceptualization and design of a clinical study: Part 2. Indian J Psychol Med 2021;43(3):265–268. DOI: 10.1177/0253717621996151.
26. Mishra P, Singh U, Pandey CM, et al. Application of Student's t-test, analysis of variance, and covariance. Ann Card Anaesth 2019;22(4):407–411. DOI: 10.4103/aca.ACA_94_19.
27. Nahm FS. Nonparametric statistical tests for the continuous data: the basic concept and the practical use. Korean J Anesthesiol 2016;69(1):8–14. DOI: 10.4097/kjae.2016.69.1.8.
28. Shih JH, Fay MP. Pearson's chi-square test and rank correlation inferences for clustered data. Biometrics 2017;73(3):822–834. DOI: 10.1111/biom.12653.
29. Kim HY. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. Restor Dent Endod 2017;42(2):152–155. DOI: 10.5395/rde.2017.42.2.152.
30. Kwak S. Are only p-values less than 0.05 significant? A p-value greater than 0.05 is also significant! J Lipid Atheroscler 2023;12(2):89–95. DOI: 10.12997/jla.2023.12.2.89.
31. Fenn-Moltu S, Fitzgibbon SP, Ciarrusta J, et al. Development of neonatal brain functional centrality and alterations associated with preterm birth. Cereb Cortex 2023;33(9):5585–5596. DOI: 10.1093/cercor/bhac444.
32. Brummelte S, Grunau RE, Chau V, et al. Procedural pain and brain development in premature newborns. Ann Neurol 2012;71(3):385–396. DOI: 10.1002/ana.22267.
33. Taddio A, Katz J, Ilersich AL, et al. Effect of neonatal circumcision on pain response during subsequent routine vaccination. Lancet 1997;349(9052):599–603. DOI: 10.1016/S0140-6736(96)10316-0.
34. Victoria NC, Murphy AZ. Exposure to early life pain: Long term consequences and contributing mechanisms. Curr Opin Behav Sci 2016;7:61–68. DOI: 10.1016/j.cobeha.2015.11.015.

35. Rawal S, Ghai A, Jindal T. Twenty-five percent dextrose and EBM in pain relief during heel lance in late preterm babies using the PIPP score: A randomized controlled trial. J Neonatol 2018;32(2–3):43–49. DOI: 10.1177/0973217918795027.
36. Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. Pediatr Res 2014;75(5):584–587. DOI: 10.1038/pr.2014.16.
37. Grunau RE. Neonatal pain in very preterm infants: Long-term effects on brain, neurodevelopment and pain reactivity. Rambam Maimonides Med J 2013;4(4):e0025. DOI: 10.5041/RMMJ.10132.
38. Shanthi Y, Thandapani K, Krishnakumar R, et al. Efficacy of 10% dextrose versus expressed breast milk in relieving procedural pain in neonates: A randomized controlled trial. J Clin Neonatol 2024;13(3):90–94. DOI: 10.4103/jcn.jcn_37_24.
39. Stevens BJ, Gibbins S, Yamada J, et al. The premature infant pain profile-revised (PIPP-R): Initial validation and feasibility. Clin J Pain 2014;30(3):238–243. DOI: 10.1097/AJP.0b013e3182906aed.
40. Dasari S, Subramanian P, Maruthi EB, et al. To compare the effect of expressed breast milk (EBM) versus 10% dextrose on procedural pain in term neonates: A double-blind randomized control trial in a rural teaching hospital in Telangana. Int J Pharm Clin Res 2024;16(7):95–101.
41. Jha L, Kumar VN, Banerjee S, et al. Efficacy of enhanced dose of expressed breast milk in neonatal procedural pain relief: A randomised placebo-controlled study. Indian J Neonatal Med Res 2023;11(2):PO01–PO05. DOI: 10.7860/IJNMR/2023/59294.2377.
42. Bueno M, Ballantyne M, Campbell-Yeo M, et al. A longitudinal observational study on the epidemiology of painful procedures and sucrose administration in hospitalized preterm neonates. Paediatr Neonatal Pain 2024;6(1):10–18. DOI: 10.1002/pne2.12114.
43. Nimbalkar S, Sinojia A, Dongara A. Reduction of neonatal pain following administration of 25% lingual dextrose: A randomized control trial. J Trop Pediatr 2013;59(3):223–225. DOI: 10.1093/tropej/fms072.
44. Nesargi SV, Nithyanandam S, Rao S, et al. Topical anesthesia or oral dextrose for the relief of pain in screening for retinopathy of prematurity: A randomized controlled double-blinded trial. J Trop Pediatr 2015;61(1):20–24. DOI: 10.1093/tropej/fmu058.
45. Chermont AG, Falcao LF, de Souza Silva EH, et al. Skin-to-skin contact and/or oral 25% dextrose for procedural pain relief for term newborn infants. Pediatrics 2009;124(6):e1101–e1107. DOI: 10.1542/peds.2009-0993.
46. Acharya S, Koul P, Pokhrel S, et al. Efficacy of 25% dextrose versus breast milk on pain and duration of cry during heel prick in neonates: A systematic review and meta-analysis. J Integr Nurs 2024;6(4):209–217. DOI: 10.4103/jin.jin_74_24.

CASE SERIES

Neonatal Tuberculosis in Preterm Infants Admitted to a Neonatal Intensive Care Unit in the United Arab Emirates

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Abstract

Introduction: Congenital tuberculosis is a rare but serious form of tuberculosis that occurs due to intra- or perinatal transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*) from an infected mother to the fetus/infant. We present cases of three premature infants treated at our unit.

Clinical features:

Case 1: A significantly ill mother delivered a female infant at 27 weeks, who tested negative in her initial screening for tuberculosis. However, she deteriorated on postnatal day 40, and the gastric aspirates showed acid-fast bacilli (AFB). There was a good clinical response to antituberculosis treatment.

Cases 2 and 3: Our second and third patients were dichorionic-diamniotic twins born at 26^{+5} weeks' gestation.

Twin 2 was on minimal respiratory support until postnatal day 37, when he worsened despite antibiotic therapy; the cultures remained negative. Gastric aspirates for AFB were positive. Once the diagnosis of TB was confirmed in this twin, gastric aspirate samples from twin 1 were tested for AFB but showed inconclusive results. The infant developed progressively worsening respiratory distress on postnatal day 50; he showed a good clinical response to empiric antituberculosis treatment.

Conclusion: Congenital tuberculosis can present with a myriad of signs/symptoms that are often nonspecific. There can be important hints in maternal history and clinical deterioration despite conventional antibiotics. These infants then need to be evaluated specifically for mycobacterial infections.

Keywords: Congenital tuberculosis, Neonatal tuberculosis, Perinatal tuberculosis, Preterm, Neonatal intensive care unit.

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Introduction

Tuberculosis infections remain a serious health burden, with more than 10.8 million cases reported worldwide in 2023.[1] Of these, around 67% are reported from about 10 countries in Southeast Asia and Africa. Children less than 14 years old account for 12% of these cases.[1] Tuberculosis in the neonatal age-group remains largely underdiagnosed and underreported, with fewer than 500 reported cases worldwide.[2]

The authors present three cases managed at a tertiary-level neonatal intensive care unit (NICU) in the United Arab Emirates (UAE). The manuscript has been approved by the institutional review board.

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Case 1 (Table 1)

A 27-week gestation, 830 gm, female infant born by cesarean section to an unwell mother, who was later diagnosed as having disseminated tuberculosis. The infant's acid-fast bacilli (AFB) staining, culture and polymerase chain reaction were negative on the fifth day.[3,4] The infant remained clinically well until postnatal day 40, when she developed worsening apnea and respiratory distress (Fig. 1). A sepsis work-up was done, and she was started on antibiotics in view of respiratory support. Her clinical condition continued to deteriorate with worsening inflammatory markers despite negative cultures and a respiratory viral panel. A repeat gastric aspirate sample turned out to be positive for AFB staining. A blood interferon-gamma release assay test was also positive.[5] First-line antituberculosis (AT) therapy was initiated, and there was clinical and laboratory improvement by the end of the first week of treatment. She was discharged on antituberculosis treatment at 43 weeks' post-menstrual age (PMA).

Cases 2 and 3 (Table 1)

Our second and third patients were dichorionic-diamniotic twins. They were born to a mother who underwent treatment for primary infertility and was asymptomatic; she had presented with preterm labor at 26^{+5} weeks.

Twin 2

Initial course in NICU was unremarkable. He was on minimal respiratory support until day 37 of life when he developed worsening respiratory distress and required escalation of respiratory support (Fig. 2). A sepsis work-up for late-onset infections was done, and antibiotics were started. However, she continued to

Table 1: Clinical and laboratory profile of the premature infants

Clinical details	*Case 1*	*Case 2*	*Case 3*
Gestational age (weeks)	27	26^{+5}	26^{+5}
Weight (gms)	830	1,020	1,040
Maternal history	33 years, primigravidae, African, no antenatal care, presented with breathlessness, abdominal pain, and swelling over the feet; diagnosed as pulmonary tuberculosis on the fifth day of admission. Delivered by CS. Placental histopathology not done. Mother died on the fourth day of admission	36 years, primigravidae, African, *In vitro* fertilization, dichorionic diamniotic twins, no general symptoms. Delivered by CS due to fetal distress. Placental histopathology was not done. Subsequently screened and diagnosed as having pulmonary tuberculosis, after diagnosis of the twins. She received treatment for the same	
Onset of symptoms (days)	40	37	50
Total white blood cell count (10^9/L)	16.45	13.59	29.5
Absolute neutrophil count (10^9/L)	5.72	7.59	16.01
Platelet count (10^9/L)	298	291	229
Serial C-reactive protein (mg/L)	46, 59, 72, 28, 10	35, 65, 98, 126, 10	<0.6, 66, <0.6
Gastric aspirate—Acid-fast bacilli smear	Positive	Positive	Inconclusive: 1–2 AFB/300 fields
Gastric aspirate—Mycobacteria culture	Negative	Positive	Negative
Tuberculosis polymerase chain reaction	Negative	Negative	Negative
Quantiferon TB gold test	Positive	Not done	Intermediate
Cerebrospinal fluid analysis	Normal	Normal	Normal
Chest X-ray	Bilateral granular opacities. Left > right	Bilateral granular opacities	Bilateral granular opacities with cystic changes
Computerized tomography chest	Left lower lobe—cavity with consolidation Right upper lobe—fibrotic changes and consolidation	Not done	Not done
Treatment	Isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months, followed by isoniazid and rifampicin for 7 months. No steroids	Isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months, followed by isoniazid and rifampicin for 7 months. No steroids	Isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months, followed by isoniazid and rifampicin for 7 months. No steroids
Outcome	Discharged. No adverse effects of the antituberculosis treatment were noted	Discharged. No adverse effects of the antituberculosis treatment were noted	Discharged. No adverse effects of the antituberculosis treatment were noted

show clinical deterioration with worsening inflammatory markers. Cultures and the respiratory viral panel remained negative. At this point, the diagnosis of TB was considered. The gastric aspirates were positive for AFB in smear and culture. First-line antituberculosis treatment was started, and there was clinical and laboratory improvement by 14 days. He was discharged on AT treatment at 41 weeks PMA.

Twin 1

The infant was asymptomatic but was evaluated for tuberculosis when his twin was diagnosed to have congenital tuberculosis. Gastric aspirate samples were sent for screening of AFB, one of which was reported inconclusive; there were 1-2 AFB/300 fields. However, by postnatal day 50, he began to show signs of worsening respiratory distress and similar radiological signs as his sibling (Fig. 3). His blood Interferon gamma release assay was intermediate-positive. He was started on antituberculosis treatment, and showed dramatic clinical improvement in a week. He was also discharged on antituberculosis drugs at 41 weeks' PMA.

All three reported infants were isolated after the confirmation of their diagnosis. Other infants admitted to the NICU at that time were screened and again 3 months later with a tuberculin skin test and a chest X-ray; all tested negative. All exposed healthcare providers were evaluated clinically and screened by skin tests and did not show signs of infection.

Discussion

In this article, we report three premature infants with congenital tuberculosis with pulmonary manifestations. This is a rare but

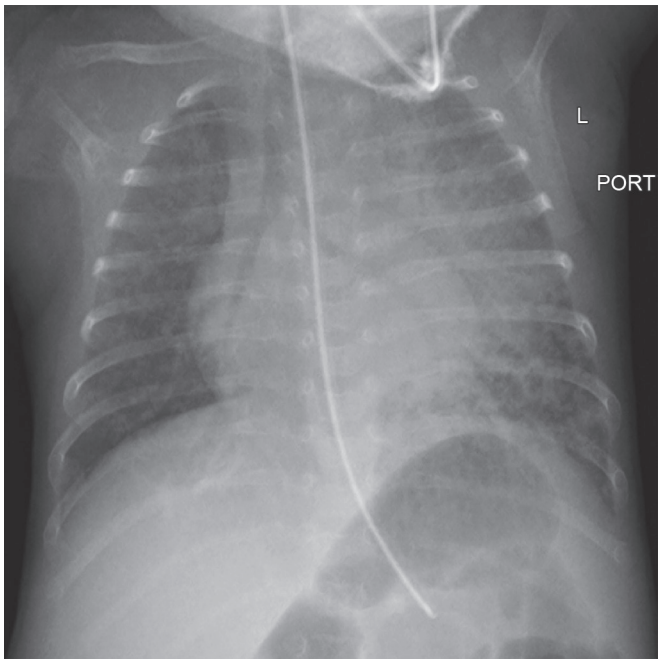

Fig. 1: Chest X-ray of case 1 showing bilateral granular opacities, more on the left

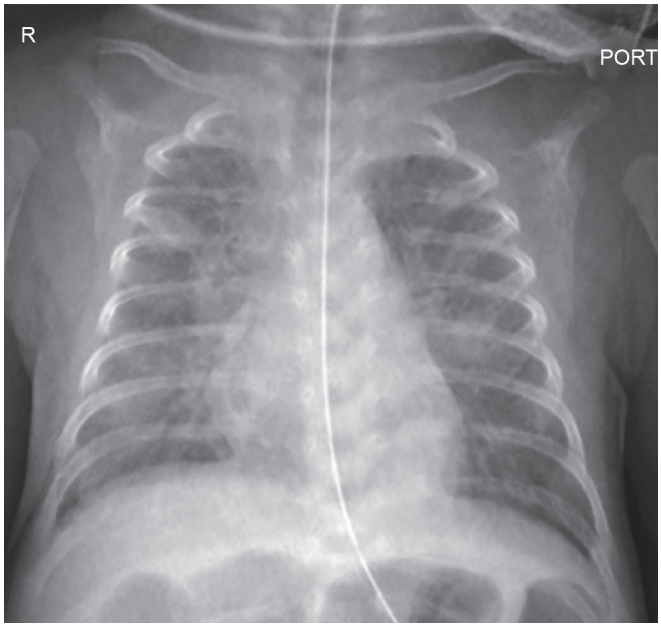

Fig. 2: Chest X-ray of case 2 showing bilateral granular opacities

serious form of tuberculosis that occurs due to intra- or perinatal transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*). Neonatal TB can be conventionally differentiated into perinatal and congenital TB. In congenital TB, there is intrauterine transmission through the umbilical vein or by aspiration/ingestion of contaminated amniotic fluid in the intrauterine period.[3–5] Cantwell's criteria are conventionally used to differentiate between congenital and perinatal TB. Cantwell's criteria include a proven tuberculosis lesion in the infant and one of the following criteria: (a) Lesions in the first week of life; (b) Primary hepatic complex/caseating hepatic granuloma; (c) TB infection of the placenta/maternal genital tract; (d) Exclusion of TB in contacts.[6] In perinatal TB, *M. tuberculosis* is spread to the neonate by ingestion/inhalation of droplets, or by direct contact with the infected genital tract. The source can be the mother or any other infected person in the peripartum period.[3] In all three cases, TB lesions in infants were proven, but liver and placental/urogenital biopsy were not done. The infants presented later than 1 week. Post/perinatal transmission cannot be ruled out definitively. Failure to differentiate into perinatal or congenital TB has no diagnostic or therapeutic implications.

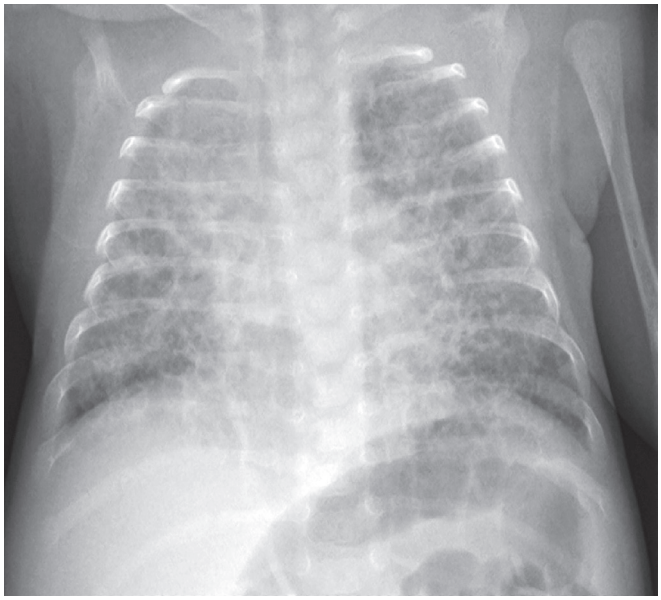

Fig. 3: Chest X-ray of case 3 showing bilateral granular opacities with cystic changes

Maternal tuberculosis can often remain undiagnosed or be asymptomatic, and hence, congenital tuberculosis is often overlooked during the neonatal period.[7] Pregnancy can be an immunocompromised situation and is associated with TB. World Health Organization recommends routine testing for TB during pregnancy in areas with an incidence >100/1,00,000 by a screening questionnaire—(a) cough lasting >2 weeks, or (b) cough of any duration/hemoptysis/weight loss/fever, night sweats, or a shielded chest X-ray.[8,9] Rampant use of *in vitro* fertilization with improper initial workup has also been associated with an increase in the incidence of neonatal tuberculosis.[10] As happened in our cases, the diagnosis of the mother is mostly established after the infant is diagnosed.[8] Tuberculosis in pregnancy can increase the risk of adverse outcomes like prematurity, low birth weight, birth asphyxia, and perinatal death.[11]

The incidence of tuberculosis in the UAE has been low. In 2,000, the rates were reported as 4.2 per 1,00,000, and these declined to around 0.75–0.80 per 1,00,000 in the 2014–2017 period.[12] In 2023, data from the World Bank approximated the rates around 0.8 cases per 1,00,000 population.[1] These low rates may be rooted in strong public health strategies with surveillance, screening, diagnostic programs, and newborn BCG vaccination. Around 85% of the total population of the UAE is expatriates, and many have immigrated from countries with a high incidence of tuberculosis.[13] Considering this unique socio-demographic profile, there is a need for physicians to be vigilant.

In congenital tuberculosis, infants typically manifest with clinical features within the first few weeks of life, although some severely afflicted cases may manifest earlier.[14] Patients may present with fever, respiratory distress, lethargy, poor feeding, hepatosplenomegaly, abdominal distension, or failure to thrive. Some may develop meningitis, disseminated tuberculosis, respiratory failure, shock, disseminated intravascular coagulation, or multiorgan failure.[11] Most of these symptoms overlap with conditions like sepsis-bacterial/viral/fungal or chronic lung disease.[15] The authors suggest maintaining a high index of suspicion in cases not responding to conventional treatment, where there is progressive clinical deterioration, elevated inflammatory markers, and in infants of mothers belonging to countries with a high incidence of tuberculosis.[14] The diagnosis of pre-/perinatal tuberculosis is established by demonstrating acid-fast *M. tuberculosis* in specimens such as gastric aspirates, liver or lymph node biopsies, and cerebrospinal fluid.[16] However, these tests are operator-dependent and can have a long turnaround time, even up to 6 weeks. Information about maternal disease, with placental or genital tract involvement, can raise the index of suspicion.[17] Blood interferon gamma release assay and Tuberculin skin test work on similar principles, but sensitivity and specificity in neonates remain low.[5,8] Tuberculosis polymerase chain reaction is a useful diagnostic tool which, like culture, can also provide information on drug susceptibility.[18] More invasive procedures like ascitic/pleural fluid tapping, lymph-node biopsy, and liver biopsy are done only if other investigations identify a focus.[19] Chest X-ray may show some abnormality in some patients, but the findings are non-specific and can overlap with those of chronic lung disease in premature infants.[4]

The first-line management of neonates with tuberculosis involves using a multidrug regimen comprised of specific drugs such as rifampicin, isoniazid, pyrazinamide, and ethambutol (RIPE).[20] Second-line drugs are reserved for special situations.[21] The treatment is typically continued for 6–12 months.[5,8] Early recognition is critical, as congenital tuberculosis can be lethal without prompt intervention.[22] Multi- or extensively-drug-resistant *M. tuberculosis* bacilli have not been seen frequently in neonates so far, but neonatal TB continues to have a high morbidity and mortality.[23] Poor prognosticators include neonates who present <21 days of age, have intracranial lesions, leukopenia, and chest X-ray suggesting a miliary pattern.[23]

Conclusion

Congenital tuberculosis remains rare and underdiagnosed. A high index of suspicion is necessary to establish the diagnosis. Timely diagnosis and treatment can improve outcomes.

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References

1. WHO. Global Tuberculosis Report 2024: TB incidence. Geneva: World Health Organization; 2025. Available from: https://www.who.int/teams/global-programme-on-tuberculosis-and-lung-health/tb-reports/global-tuberculosis-report-2024/tb-disease-burden/1-1-tb-incidence.
2. Ryu BH, Baek EH, Kim DH, et al. Preterm twins born to a mother with miliary tuberculosis: Importance of early recognition and prompt response in infection control to manage congenital tuberculosis exposure in a neonatal intensive care unit. Jpn J Infect Dis 2021;74(2):97–101. DOI: 10.7883/yoken.JJID.2020.183.
3. Tomar R, Gupta A, Prasad TR, et al. Congenital tuberculosis. Med J Armed Forces India 2008;64(1):78–80. DOI: 10.1016/S0377-1237(08)80160-8.
4. Schaaf HS, Bekker A, Rabie H. Perinatal tuberculosis: An approach to an under-recognized diagnosis. Front Public Health 2023;11:1239734. DOI: 10.3389/fpubh.2023.1239734.
5. Shao Y, Hageman JR, Shulman ST. Congenital and perinatal tuberculosis. Neoreviews 2021;22(9):e600–e605. DOI: 10.1542/neo.22-9-e600.
6. Cantwell MF, Shehab ZM, Costello M, et al. Congenital tuberculosis. N Engl J Med 1994;330(15):1051–1054. DOI: 10.1056/NEJM199404143301505.
7. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. Obstet Gynecol 2020;135(6):1444–1453. DOI: 10.1097/AOG.0000000000003890.
8. Snow KJ, Bekker A, Huang GK, et al. Tuberculosis in pregnant women and neonates: A meta-review of current evidence. Paediatr Respir Rev 2020;36:27–32. DOI: 10.1016/j.prrv.2020.02.001.
9. Ali RF, Siddiqi DA, Malik AA, et al. Integrating tuberculosis screening into antenatal visits to improve tuberculosis diagnosis and care: Results from a pilot project in Pakistan. Int J Infect Dis 2021;108:391–396. DOI: 10.1016/j.ijid.2021.05.072.
10. Zhang X, Zhuxiao R, Xu F, et al. Congenital tuberculosis after *in vitro* fertilization: Suggestion for tuberculosis tests in infertile women in developing countries. J Int Med Res 2018;46(12):5316–5321. DOI: 10.1177/0300060518808179.
11. Peng W, Yang J, Liu E. Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009. Pediatr Pulmonol 2011;46(12):1215–1224. DOI: 10.1002/ppul.21490.
12. WHO. World Health Organization Data. Geneva: World Health Organization Global; 2025. Available from: https://data.who.int/countries/784.
13. UAE. Facts and Figures Abu Al Abyad Street. Abu Dhabi: UAE Ministry of Foreign Affairs; 2025. Available from: https://www.mofa.gov.ae/en/the-uae/facts-and-figures.
14. Chang CW, Wu PW, Yeh CH, et al. Congenital tuberculosis: Case report and review of the literature. Paediatr Int Child Health 2018;38(3):216–219. DOI: 10.1080/20469047.2017.1315912.
15. Li C, Liu L, Tao Y. Diagnosis and treatment of congenital tuberculosis: A systematic review of 92 cases. Orphanet J Rare Dis 2019;14(1):131. DOI: 10.1186/s13023-019-1101-x.
16. Katoch VM. Advances in molecular diagnosis of tuberculosis. Med J Armed Forces India 2003;59(3):182–186. DOI: 10.1016/S0377-1237(03)80001-1.
17. Pop LG, Bacalbasa N, Suciu ID, et al. Tuberculosis in pregnancy. J Med Life 2021;14(2):165–169. DOI: 10.25122/jml-2021-0001.
18. Gholoobi A, Masoudi-Kazemabad A, Meshkat M, et al. Comparison of culture and PCR methods for diagnosis of mycobacterium tuberculosis in different clinical specimens. Jundishapur J Microbiol 2014;7(2):e8939. DOI: 10.5812/jjm.8939.
19. Vorster MJ, Allwood BW, Diacon AH, et al. Tuberculous pleural effusions: Advances and controversies. J Thorac Dis 2015;7(6):981–991. DOI: 10.3978/j.issn.2072-1439.2015.02.18.
20. WHO. Treatment of tuberculosis patients. 2. Geneva: World Health Organization; 2008.
21. Ramachandran G, Swaminathan S. Safety and tolerability profile of second-line anti-tuberculosis medications. Drug Saf 2015;38(3):253–269. DOI: 10.1007/s40264-015-0267-y.
22. Saramba MI, Zhao D. A perspective of the diagnosis and management of congenital tuberculosis. J Pathog 2016;2016:8623825. DOI: 10.1155/2016/8623825.
23. Lhadon T, Jullien S. Congenital multidrug-resistant tuberculosis in a neonate: A case report. J Trop Pediatr 2019;65(2):188–191. DOI: 10.1093/tropej/fmy020.

REVIEW ARTICLE

Transgenerational Epigenetics

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Abstract

Transgenerational epigenetic inheritance is the transmission of epigenetic modifications and markers from one generation to at least two subsequent generations of offspring without altering the primary structure of DNA. It differs from intergenerational transmission of epigenetic marks due to continued exposure of gametes or embryos to environmental factors. The best-studied epigenetic marks include DNA methylation, histone modifications, non-coding RNAs, and chromatin structural changes. Records from the Överkalix cohort in northern Sweden and the Dutch Hunger Winter have provided multigenerational demographic and health data with strong evidence for intergenerational epigenetic effects. In rodent studies, endocrine disruptors, pesticides, and nutritional deficiencies associate ancestral exposures to altered metabolism, fertility, and disease risk in unexposed descendants across generations. Transgenerational epigenetics is a rapidly evolving field that challenges traditional views of inheritance by suggesting that environmentally induced epigenetic information can persist beyond direct exposure and influence phenotypes across generations. However, even though there is compelling evidence from animal models for germline transmission of epigenetic marks, human clinical data are still limited and are often confounded by intergenerational effects and environmental continuity.

Keywords: Across indirect epigenetics (AIE), Agouti viable yellow (Avy/a) mouse, Bisphenol A (BPA), Chemical tags, Direct epigenetics, DNA methylation, Dutch Hunger Winter study, Epigenetics, Gene expression, Heritable, Infant, Inherited, Intergenerational inheritance, Metabolic reprogramming, Metastable epialleles, Molar or top down epigenetics, Molecular or bottom-up epigenetics, Neonate, Newborn, Paramutation, Polymorphisms, Polyphenisms, Post-translational modification, Post-translational modifications, RNA silencing, Soft inheritance, Transgenerational epigenetic variation, Transgenerational inheritance, Vinclozolin, Within indirect epigenetics (WIE).

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Key Points

- Transgenerational epigenetics refers to germline-mediated transmission of epigenetic marks across generations in the absence of continued exposure, distinguishing it from intergenerational effects due to direct exposure of gametes or embryos.
- Soft inheritance is the inheritance of acquired characteristics or environmentally induced traits without changes in the DNA sequence, whereas hard inheritance refers to Mendelian, DNA-based genetic inheritance.
- Germline-dependent epigenetic modifications are stably transmitted through the germline (spermatozoa or oocyte) to the next generation. Context-dependent epigenetic modifications are induced by environmental or physiological factors and are generally reset during germline formation or early embryogenesis.
- Persistence of epigenetic information involves incomplete erasure during germline reprogramming, epigenetic re-establishment guided by small RNAs, or chromatin-based memory, enabling stable propagation of altered states.
- Understanding the molecular stability, environmental triggers, and health consequences of transgenerational epigenetic inheritance may reshape our understanding of disease etiology, evolution, and preventive public health strategies.

Introduction

Transgenerational epigenetic inheritance is the transmission of epigenetic markers and modifications from one generation to at least two subsequent generations of offspring without altering the primary structure of DNA.

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History of Epigenetics

Preformationism vs Epigenesis

In the 16th–17th century, investigators were divided by their beliefs of preformationism vs epigenesis. Preformationists, including August Weissman, believed that the eggs contained all genes to determine the future phenotype. In a well-known study, he amputated the tails of several generations of mice; the inference was the "Weismann barrier", in which genetic information is transmitted to progeny by germline cells and not somatic cells.

Epigenesis was a concept first introduced by Jean-Baptiste Lamarck and Charles Darwin, who suggested that morphological traits reflect the interaction of the genetic constituents of the zygote with the environment.[1] Lamarck initially postulated that species could inherit acquired traits favorable to their survival, which was later dismissed after Darwin's theory of descent with modification. The word "epigenetics" was coined by Conrad Waddington; this was a new branch of biology focused on causal interactions between genes and their products, which "bring the phenotype into being."[2] The classical definition of epigenetics was proposed later, as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence."[3] DNA methylation and chromatin modifications of histone tails can lead to condensation of chromatin with "repressive" states, or increased accessibility and "permissive" states.[3]

Soft Inheritance

Soft inheritance is a term used to describe the inheritance of acquired characteristics or environmentally induced traits, without changes in the DNA sequence.[4] Ernst Mayr (1904–2005) first proposed the term "soft inheritance." It contrasts with "hard inheritance," which refers to Mendelian, DNA-based genetic inheritance.

Soft inheritance is viewed by evolutionary biologists as an adaptive process that can be advantageous to the individual or species. These epigenetic changes could be relatively stable and perpetuate gene expression, possibly adding a survival benefit in the continuously changing environment. Adaptive parental effects are one example of soft inheritance. The gradual loss/resetting of these epigenetic marks over generations can dilute these beneficial changes.

The internal environment, even *in utero*, interacts with the external environment with both immediate and life-long consequences. Epigenetic reactions/consequences often get amplified through higher levels of biological organization with readily notable functional differences, phenotypic changes, and responses to the environment.[5]

Molecular vs Molar Epigenetics

One way to study epigenetics is in a reductionist, molecular view of altered gene expression. It focuses on transcriptional and translational control. The other, the so-called molar epigenetics, centers on evolution and adaptive significance. This approach emphasizes the individual's interactions with its biotic and physical environment over time (Table 1 and Fig. 1).[1]

Individuals are influenced by environmentally induced epigenetic modifications beginning early, before/after birth. These early changes are important because of the plasticity of molecular epigenetic processes during these periods. The time of maximal neuronal plasticity is in the earliest stages of development, beginning in utero; the endocrine and environmental stimuli can induce importance during these periods.[6]

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Saltation

Étienne Geoffroy Saint-Hilaire first endorsed a theory of saltational evolution.[7] Goldschmidt called deleterious macromutations "monsters" and believed that macroevolution proceeds by natural selection instead of the culmination of small changes within populations. Such macromutations can intercede with epigenetic processes and affect the causal processes in biological development.[8] Saltational evolution pertains to natural selection and adaptive evolution rather than small genetic mutations.

Table 1: Molecular vs molar epigenetics

Aspect	*Molecular epigenetics*	*Molar epigenetics*
Level	Cellular/gene	Whole organism/behavioral
Focus	Mechanistic regulation	Environmental and developmental effects
Methods	Molecular biology, sequencing	Behavioral studies, epidemiology
Timescale	Immediate/short-term	Developmental/lifespan
Goal	Explain how marks control genes	Explain how the environment shapes the phenotype

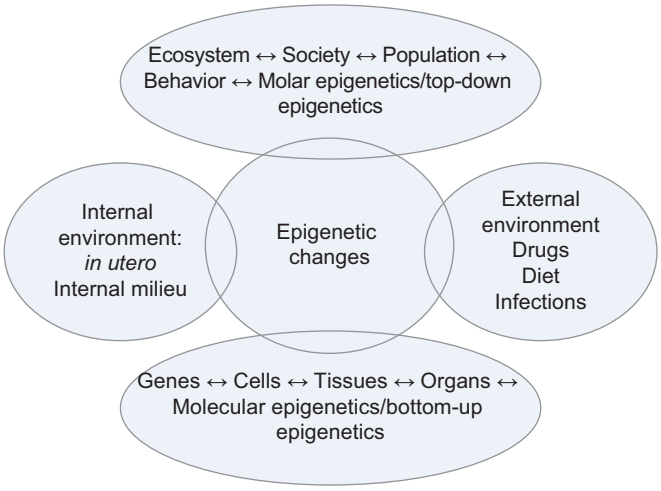

Fig. 1: Contribution of internal and external environment on epigenetic changes shown in a radian Venn diagram. There are two major considerations in viewing epigenetics, molar and molecular

Epigenetic Memory

Heritable traits carry a potential to be passed to the subsequent generations; the term encompasses genetic or epigenetic, context dependent or mitotic epigenetic modifications.

Inherited traits have already been transmitted. This description is usually reserved for classic, genetic mechanisms originating in germline epigenetic modifications. In meiotic or germline-dependent epigenetic modifications, the epigenetic imprint has become integrated in the germline, is independent of exposure to the original causative agent, and is therefore transmitted to successive generations.[9–12] Table 2 illustrates frequently used definitions in transgenerational epigenetics.

During development, DNA methylation patterns of most genes are first erased, and then re-established during embryogenesis. Specific methylation patterns of heritable epi-alleles are maintained in the individual and are also passed through to subsequent generations; these might be differentially expressed in male and female gametes.[13] Environmental exposures often induce transient changes in somatic cells that are seen for the duration of exposure. In germline cells, these changes might persist even after the cells are

Table 2: Definitions

Canalization	Developmental process proposed by Waddington by which the cell, tissue, organ, or organism initially is subject to internal and external forces but, through time, is less subject to influences from these forces, ultimately leading to reduced variability in naturally occurring species.
Context-dependent epigenetic modification	Epigenetic modification caused by experiences during sensitive periods of life (prenatal, early postnatal, adolescence) that modify the biological system but that are not intrinsically heritable in the absence of continued exposure. Such experiences can include passive or active exposures and have long-lasting effects on the individual's subsequent life history. These modifications can be perpetuated across generations due to the persistence of the causal environmental factor, such that each generation is exposed to the same conditions.
Endocrine-disrupting chemical (EDC)	Anthropogenic chemical(s) that interfere(s) with any aspect of hormone action.
Epialleles	A group of otherwise identical genes that differ in the degree of methylation and produce novel phenotypes that are heritable across generations.
Epigenetics	Epigenetics as a field of study refers to the analysis of changes that can occur on chromatin and DNA that are heritable and do not affect the primary DNA sequence.
Epigenome	The epigenome is the collection of all of the epigenetic marks on the DNA in a single cell.[14]
Epigenomics	Epigenomics refers to the analysis of epigenetic changes across the whole genome in a cell or entire organism.[14,15] In a multi-cellular organism, each cell type will be characterized by the same genome, along with as many epigenomes as there are distinct cell types.
Epigenotype	A term coined by Waddington to suggest a process by which a cell may differentiate as a consequence of changes in the internal and external environments; a potential for change that is heritable and the basic genetic program of that cell. Refers to a stable pattern of gene expression that is outside the actual base pair sequence of DNA.[1]
Epiphenotype	A concept developed by E.O. Wiley as a means to evaluate the total or essential characters of an individual at any point in time in its life history.[1]
Epigenetic modification	An epigenetic modification (epigenetic change, epigenetic mark) is a chemical alteration to DNA or chromatin that does not affect the primary DNA sequence. They refer to chromatin and DNA modifications that influence genome function but do not change the underlying DNA sequence.
Epigenetic effects	Changes in the phenotype and/or specific traits that result from the environmental modification of the molecular factors and processes around DNA that regulate genome activity, yet are independent of the DNA sequence.
Epigenetic regulation	Epigenetic regulation refers to the regulation of gene expression by epigenetic modifications.
Epigenetic epidemiology	Epigenetic epidemiology is a field of study that seeks to evaluate the effects of epigenetic changes in populations of individuals, such as cohorts of people who were exposed to conditions that might alter epigenetic regulation (famines, toxins, and shifts in dietary intake).
Epistasis	Traits that depend upon more than one gene, each interacting with one another.
Genetic assimilation	A concept attributed to Waddington in which phenotypes that are environmentally malleable become genetically fixed and no longer require the original environmental stimulus in order to be manifested.
Germline-dependent epigenetic modification	Epigenetic modification arising from exposure to an environmental cue during germline development. By being incorporated into the germline, the effect is manifested each generation, even in the absence of continued exposure to the causative agent.
Homeorhesis	Stability of the process of development.
Homeostasis	Stability of a final steady state.

(Contd...)

Table 2: *(Contd...)*

Heritable	An epigenetic mark or phenotype has the capacity to be transmitted through the germline across multiple generations. It emphasizes potential transmissibility.
Inherited	An epigenetic mark or phenotype is actually observed in descendants who were never directly exposed to the original stimulus. It reflects the demonstrated transmission of the epigenetic information across generations.
Soft inheritance	The generation of a new phenotype is less rigidly determined and shows a more rapid response to the environment.[4]
Hard inheritance	Essentially Mendelian; hereditary material remains constant between generations (except for rare random mutations).[4]
Intergenerational inheritance	Transmission of biological effects (such as epigenetic changes, environmental exposures, or stress effects) from parents (F0) directly to their children (F1).
Transgenerational inheritance	Transmission of biological effects to subsequent generations (F2, F3, etc.) that were never directly exposed to the original environmental factor.
Transgenerational epigenetic effects	Phenotypes present in successive generations that are not genetically determined.
Transgenerational Epigenetic inheritance or gametic epigenetic inheritance	A phenotype present in successive generations that is nongenetically determined and results from epigenetic modifications passed via the gametes that escape reprogramming.
Molecular or bottom-up epigenetics	Molecular epigenetics revolves around gene expression alterations and molecular levels of analysis. The object of study in molecular epigenetics is transcriptional and translational control.[1]
Molar or top-down epigenetics	Molar epigenetics centers on evolution and adaptive significance as perceived by psychobiology and evolutionary biology. The object of study in *molar* epigenetics is the individual's interactions with its biotic and physical environment through time.[1]
Polymorphisms	Genetically based differences in a population, where two or more distinct forms (morphs) exist at the same genetic locus. Each form is controlled by different alleles (DNA variants). These differences are heritable and do not change in response to the environment.
Polyphenisms	Environmentally induced alternative phenotypes from the same genotype and are epigenetic in origin. Different environments switch on different developmental pathways, creating discrete phenotypes without DNA sequence differences.
Metastable epialleles	Genetically identical alleles that are variably expressed due to epigenetic factors in genetically identical individuals. They refer to alleles at which the epigenetic state can switch, creating different phenotypes, and where the establishment is a probabilistic event.
Epimutation	Heritable epigenetic changes usually cause an observable phenotype. They refer to abnormal epigenetic patterns that can occur in response to a DNA mutation, but the term is generally used in cases without an underlying DNA sequence change.
Paramutation	Horizontal transmission of a heritable epigenetic state from one allele of a locus to the other. It refers to an interaction between the two alleles of a locus, resulting in a heritable epigenetic change of one allele induced by the other allele.
Parental effects	Effects on the phenotype of offspring that are not determined by the offspring's own genotype but by the genotype or environmental experience of its parents.
Position-effect variegation	Variegation is caused by the inactivation of a gene in some, but not all, cells of the same cell type through its abnormal juxtaposition with heterochromatin.

no longer exposed. Table 3 lists the differences between germline-dependent vs context-dependent epigenetic modifications.

Intergenerational Inheritance

Intergenerational effects are observed when exposure of an individual (F0) can directly affect their offspring (F1) and the F1 germ cells in the fetus (F2). These do not necessarily indicate epigenetic inheritance because the germline was directly exposed (Fig. 2).

Transgenerational Inheritance

Transgenerational inheritance refers to the persistence of an effect beyond generations that were directly exposed. In mammals, the evidence for transgenerational evidence includes:[16] (a) Maternal exposure during pregnancy induces phenotypic/epigenetic changes in the third generation (in F3; F0 pregnant → F1 fetus + F2 germ cells); or (b) For paternal or non-pregnant maternal exposure, the evidence is the detection of phenotype in F2 (F0 → F1

Table 3: Germline-dependent vs context-dependent epigenetic modifications

Feature	*Germline-dependent epigenetic modifications*	*Context-dependent epigenetic modifications*
Definition	Epigenetic marks that are stably transmitted through the germline (sperm or oocyte) to the next generation.	Epigenetic marks that are induced by environmental or physiological context and are generally reset during germline formation or early embryogenesis.
Inheritance	Transgenerational inheritance is possible—passed to offspring even if they are not directly exposed to the original stimulus.	Not inherited beyond the individual or at most the directly exposed offspring (F1).
Mechanism	Survive epigenetic reprogramming that usually erases DNA methylation and histone marks during gametogenesis and early embryogenesis.	Established somatically in response to specific contexts (nutrition, stress, toxins) and are usually erased in the germline.
Examples	Genomic imprinting (e.g. IGF2 methylation)	Dutch Hunger Winter study

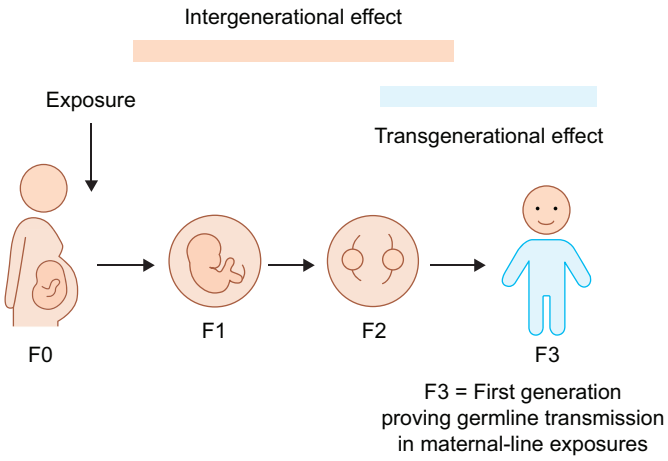

Fig. 2: Schematic showing intergenerational vs transgenerational inheritance

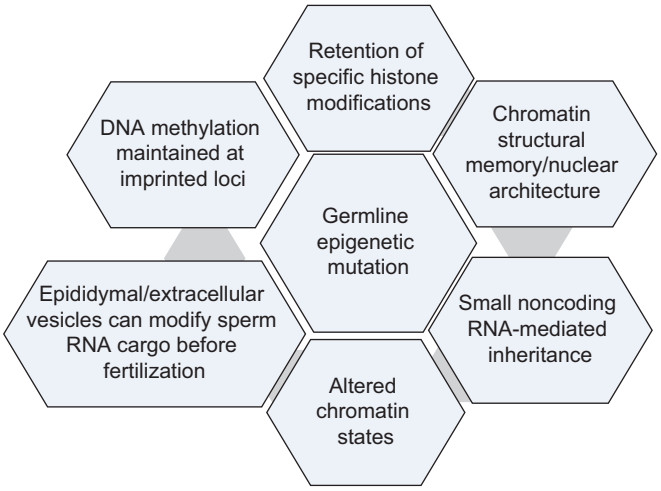

Fig. 3: Mechanisms proposed for transgenerational epigenetic inheritance shown in a hexagon radial diagram

directly exposed via gamete). Broadly, transgenerational changes show inheritance of the same epimutation and changes in gene expression across generations.

The most frequent molecular mechanisms underlying epigenetic changes beginning as early as the embryonic/fetal period include (Figs 3 and 4):[17]

- DNA methylation at CpG sites; these can sometimes escape genome-wide reprogramming, such as imprinting of control regions and metastable epialleles (MEs). MEs are stable genomic regions established stochastically in genetically identical individuals during early development with varying DNA methylation and maintained throughout life; these can produce stable epigenetic and phenotypic differences;
- Specific chemical modifications in histones;
- Small RNAs (tRNA fragments, miRNAs, piRNAs);
- Altered chromatin structure and transposable elements;
- Extracellular vesicles that can modify RNA cargo.

DNA methylation patterns are most frequently erased and reset either in the early embryo or in developing germ cells at the time of gonadal sex determination. These changes likely remove most epigenetic constraints to pluripotency in embryonic stem cells. One well-studied exception to this is the imprinting of genes, which retain their epigenetic DNA methylation pattern in a parent-of-origin allelic manner. Table 4 illustrates the most frequently seen mechanisms of epigenetic signal transmission.

Metabolites Affect Epigenetic Memory

Metabolites are required by many chromatin-modifying proteins. For instance, DNA methyltransferases and histone methyltransferases utilize S-adenosyl methionine (SAM) to add a methyl group to DNA or histone tails.[18] DNA demethylases such as ten-eleven translocases (TET) are regulated by fumarate, succinate, and α-ketogluterate.[19] Lysine demethylases are regulated by flavin adenine dinucleotide in the removal of methyl groups from histones. Histone acetyltransferases require acetyl-CoA for the addition of acetyl groups to histones.[20] Sirtuins interact with nicotinamide adenine dinucleotide (NADH) to promote deacetylation by histone deacetylases. ATP is required for serine/threonine kinase (ATM) phosphorylation of histones.

Possible Evidence of Epigenetic Memory seen in Human Studies

The Överkalix Cohort in Northern Sweden

These historical records of harvests and famines have provided multigenerational demographic and health data. Food availability and environmental conditions experienced by parents/grandparents during critical growth periods may possibly influence the health of

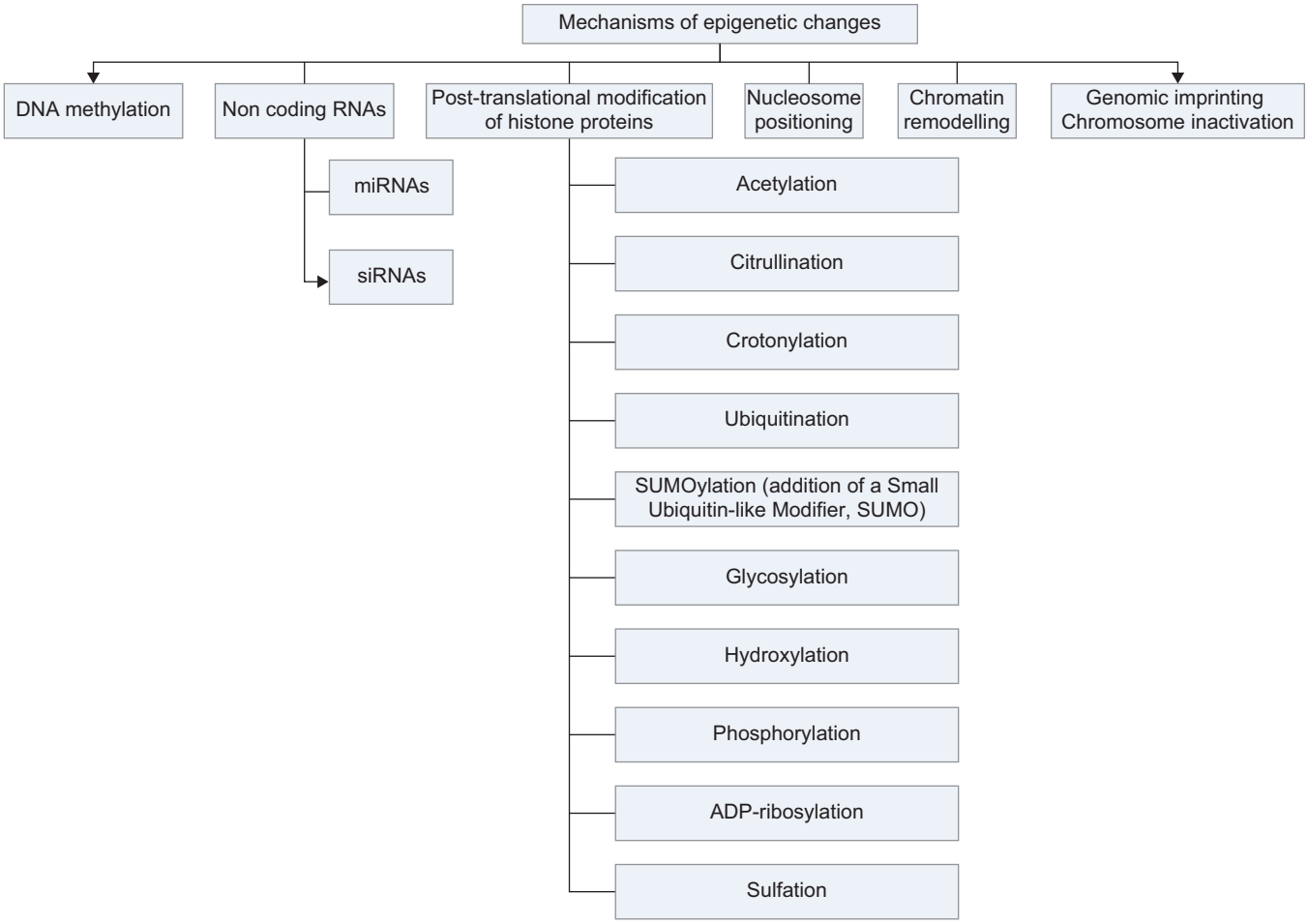

Fig. 4: Summary of major epigenetic changes shown in an organizational chart

Table 4: Toxicants associated with transgenerational epigenetic effects

Toxicant	*Observed effects*	*Generations affected*
Vinclozolin (fungicide)	Male infertility, sperm defects	F3 (in rats)
Bisphenol A (BPA)	Behavioral and metabolic changes	F3
Dioxins (TCDD)	Reproductive disorders, cancers	F3
Phthalates	Obesity, reproductive issues	F3
Pesticides (e.g. DDT)	Puberty onset changes, obesity risk	F3

their descendants. Nutritional stress or abundance during the "slow growth period" prior to puberty in one generation could alter the risk of cardiovascular disease, diabetes, and premature mortality in grandchildren. These findings provided some of the earliest human evidence for transgenerational epigenetic inheritance, suggesting that environmental exposures can leave biological imprints that extend beyond the directly exposed generation.

The Dutch Hunger Winter

A severe famine struck the German-occupied western Netherlands in 1944–1945, when a Nazi blockade cut off food supplies to millions of people. Caloric intake dropped to 400–800 calories per day, leading to widespread starvation, cold-related deaths, and long-term health consequences for survivors. The Dutch Hunger Winter studied in 2010 has shown that food restriction *in utero* had an influence on the metabolism and cardiovascular health of the offspring and resulted in an age-associated decline of cognitive functions.[21] Some babies had normal birth weights but later developed higher rates of obesity. The results show that there is a critical window during development, during which a starvation diet influences the subsequent health of the offspring. The methylation status of many genes and gene expression were altered.[22] Studies showed that prenatal exposure to malnutrition increased the risk of obesity, diabetes, cardiovascular disease, and mental health disorders later in life. There was evidence of altered DNA methylation at the *IGF2* gene. This tragic event provided important information about the Developmental Origins of Health and Disease (DOHaD) concept. The Dutch Hunger Winter study is often cited as an intergenerational, not truly transgenerational inheritance study (an additional generation needs to be tested).

It did show that the nutritional environmental effect can affect an embryo and its germline. To summarize:

- The famine-exposed fetuses (F1) showed lasting epigenetic changes, such as *IGF2* hypomethylation, and increased risk of metabolic disease in adulthood.
- Some subtle effects have been noted in their children (F2), but these are likely due to indirect developmental or maternal effects (the exposed fetus also carried its primordial germ cells that became F2), not confirmed stable epigenetic inheritance.
- No robust evidence shows these marks persisting to the F3 generation (true transgenerational inheritance) when only the F0 mother was exposed.

Poor maternal health can compromise pregnancy, leading to insulin resistance, high blood pressure, or increased glucocorticoids during pregnancy. These phenotypic changes can also be seen in the child later in life. These data suggest that some phenotypes inherited down the female line do not involve gametic epigenetic inheritance.[4]

Aging

Metabolic diseases can alter aging.[23] Epigenetic alterations such as DNA methylation profiles can also act as an "epigenetic clock."[24,25] These modifications can be accelerated or slowed by high-fat diets and caloric restriction, respectively.[25–27]

Toxicants

Upon exposure to a toxicant in a pregnant female (F0), her own somatic, fetal (F1), and fetal germ cells (which will become F2) are affected. Toxicants can alter DNA methylation, histone modifications, and ncRNA expression. These changes can silence/activate genes without altering the DNA sequence. Germline epigenetic changes that do not get erased during embryogenesis may be inherited by F3 and subsequent unexposed generations in maternal exposures, and F2 and beyond in paternal exposures.

Vinclozolin, a fungicide and an androgen-blocker, is a well-studied toxicant that induces transgenerational effects.[28–37] Bisphenol A (BPA) and Diethylstilbesterol (DES) are other toxins having transgenerational effects.[38–41]

Parental nutritional state at the time of pregnancy can also have lasting effects on immediate offspring and future descendants.

The synthetic estrogen Diethylstilbestrol (DES) was historically widely used to prevent potential miscarriages. Women exposed to DES before birth were later shown to have an increased risk of vaginal adenocarcinoma. Animal experiments showed increased tumor risk in the F2. Table 5 illustrates the common toxicants inducing transgenerational effects.

Transgenerational Epivariation

Transgenerational epivariation (TE) refers to heritable changes in epigenetic marks such as DNA methylation, histone modifications, or ncRNAs that are passed down through multiple generations without changes in the underlying DNA sequence.[42] Unlike standard genetic mutations, which alter the DNA code, epivariations alter gene expression patterns and can be reset or maintained across generations.

Animal Models of Epigenetic Memory

Transgenerational Epigenetics in Animal Models

- Agouti viable yellow mouse: Coat-color and metabolic phenotypes correlate with methylation at a ME; methyl donors in maternal diet can change offspring methylation and phenotype.
- Vinclozolin-treated rats: Fertility and endocrine effects can possibly persist to F3.
- Dietary exposures and stress in rodents: Paternal high-fat diet, low-protein diet, and/or stress can alter offspring metabolism, behavior, or gene expression via sperm small RNAs; some studies show effects across multiple generations;
- Post-fertilization transfer of viruses or toxins, possibly through the placenta or milk. Some examples may be seen in the occurrence of a gray mouse phenotype caused by a virus in milk, transplacental ethanol transfer, and undernutrition during pregnancy.
- Dam-pup behavioral interactions can perpetuate a phenotype. In rats, reduced maternal care induces a stressed phenotype in offspring; those pups become poor mothers later on in adulthood, thereby perpetuating the stressed phenotype.

Designing Transgenerational Animal Studies

A change in the F0 maternal environment, including exposure to chemical(s) that may disrupt endocrine axes, altered diet, or other stressors, can impact the developing F1 offspring(s) and primordial germ cells for the F2 generation. These extrinsic factors change during pregnancy and can directly affect the F0 through F2 generations.[43] Subsequently, studies illustrating definitive transgenerational effects in F3 and F4 generations can also be carried out.[44]

In the case of toxicant and other extrinsic exposures during gestation, the mother (F0), her growing fetus (F1), and the germ cells of fetuses that will give rise to the F2 generation are simultaneously exposed. Any effects observed in the F1 and F2 generations may be direct rather than transgenerational and context-dependent. If the *in utero* exposure alters the parenting behaviors of the F1 animals, the cognitive and developmental trajectories of their pups may be affected. These offsprings may then exhibit poor parenting, thereby creating a vicious cycle. Here, epigenetics alters phenotypes and the progression of behaviors.[45,46]

Other Factors that Might Affect Outcomes across Generations

Most transgenerational effects have been ascribed to transmission through male/female gametes.[47] Germline transgenerational effects may also be ascribed to external factors such as nutrients

Table 5: Mechanisms of epigenetic signal transmission

Replicative transmission	The signal is transmitted through meiosis in a similar manner to its mitotic maintenance.
Reconstructive transmission	The primary epigenetic signals are erased but faithfully reconstructed in the progeny based on a secondary signal.
Paramutation	A process by which epigenetic information is transmitted horizontally between alleles *in trans*. After this initial step, paramutated "epialleles" are then transmitted vertically between generations by other TEI mechanisms.

within/around the germ cells and reproductive tract, parental care provided to the various generations, and the cultural environment in which the offsprings are raised.[48]

Naturally-occurring Epigenetic/Transgenerational Animal Models

There are two distinct inherited loci where methylation pattern are associated with well-defined phenotypes. These have been seen in the *agouti* viable yellow (*Avy*) and *axin* fused (*AxinFu*) mice.[49–55] These animals are readily identifiable with a distinct external visual indicator, the color of the coat in *agouti* viable yellow (*Avy*) mice and that of the tail in *AxinFu*.

The *Avy* mice are a well-defined model of epigenetic transmission in mammals, particularly of the metabolic syndrome.[49–55] Yellow fur reflects decreased LTR methylation of the *A* gene, resulting in its constitutive expression throughout the hair cycle, and also in other organs such as the brain, pancreas, adipose tissue, and liver that do not typically express this allele.[49,50] These mice manifest maturity-onset obesity and diabetes; the risk is related to the degree of cytosine methylation of a CpG island in the 5′ long terminal repeats (LTRs).[51,52] Hypermethylation in this region results in a pseudoagouti (brown) phenotype; there is an inactive intracisternal A-particle promoter.

Maternal diet can influence the coat color and metabolic disease of progeny in *Avy/a* mice.[49,50,56] Several nutrients in the maternal diet promote epigenetic modifications of genes encoding crucial metabolic enzymes and hormones.[57–59]

Mouse agouti signaling protein (ASIP) is a 131-amino acid paracrine signaling molecule secreted during the mid-phase of the hair follicle cycle.[60] Its binding to the melanocortin receptor, MC1R, prevents alpha-MSH signaling, thereby downregulating synthesis of brown/black (eumelanin) pigments and increasing synthesis of yellow/ red (pheomelanin) pigment, resulting in production of a series of yellow bands on each hair. The escape of expression of ASIP in tissues other than the hair follicle, including the pancreas and adipose tissue in *Avy/a* mice, provides a good animal model for human metabolic disorders. In humans, ASIP is expressed in the highest amounts in the adipose tissue and in the pancreas, where it regulates various genes, including signal transducer and activator of transcription (STAT)1, STAT3, Peroxisome proliferator-activated receptor gamma (PPARG), and fatty acid synthase (FAS), which increase insulin release from pancreatic cells.[61–63] The mRNA levels of the A gene in adipose tissue are also higher in subjects with type 2 diabetes, and its protein product, ASIP, is correlated with obesity.[61–65]

In *Avy* mice, an epigenetic methylation mark located in a cryptic promoter region can be transmitted across generations.[66] Yellow-coat females on a typical chow-based (non-methyl-supplemented or methyl-deficient) diet tend to birth more yellow-coat offspring than their genetically identical brown-coat siblings. This maternal germline transmission extends through the F2 generation. A yellow-coat grandmother is more likely to have yellow-coat than brown-coat grand-offspring.[66] No paternal germline effects have been observed on coat color in these mice, suggesting that the DNA methylation marks on the *Avy* allele are maintained when passed through the oocyte but not the spermatozoa.[66]

Metastable Epialleles

Metastable epialleles can be variably expressed through epigenetic modifications in individuals with identical genetic composition.[67] The Avy mouse is an important animal model with paired phenotypes of metabolic dysfunction and coat color resulting from MEs.[68]

Paramutations

Paramutations, a transgenerational pattern of epigenetic inheritance, were first noted in plants. A trait appears dominant in an initial cross, but when the resulting offspring that would be expected to be genetically heterozygous (Aa), these would behave as AA in subsequent crosses. The dominant allele appears to convert the recessive allele into a dominant one *in trans*.[69] In maize pigmentation, a dominant paramutant *B_* allele (exhibiting transcriptional repression of the *B* transcription factor) converts its paramutable *B-I* homolog *in trans* to form a new paramutant *B_*allele (designated *B_*).[69]

Direct and Indirect Epigenetics

Direct Epigenetics

Direct epigenetic changes are seen during an individual's entire lifespan.[70] Some, such as the effects of methylation and ncRNAs, are perceived as a link between ontogenetic and phylogenetic development.[70] These changes also provide short-term regulation of gene expression by immediate-early genes such as c-fos (named after Finkel–Biskis–Jinkins murine osteogenic sarcoma virus), c-jun (cellular gene named after viral sarcoma virus oncoprotein v-Jun), EGR1 (early growth response 1), and CREB (named after DNA-binding transcriptional regulator CREB), critical regulators that can trigger adaptive transcriptional/signaling cascades.

Indirect Epigenetics

Indirect epigenetic (IE) responses occur due to the interaction between an individual and the environment. There are two IE processes: (a) within (WIE); and (b) across (AIE):[12,71]

Within indirect epigenetics begins during developmental changes *in utero*; these include all epigenetic changes that act synchronously on the developing individual. These changes are consistent with the Lamarckian theory that environmental influences or individual use/disuse of organs could cause heritable changes.

Across indirect epigenetics defines changes transmitted from previous generations. These are a faster route of transmission across generations than genetic inheritance, a concept that aligns with Lamarck's concept in a "neo-Lamarckian" way. All epigenetic changes transmitted across generations are referred to as epimutations, in contrast to classical, less frequent genetic mutations.[72] Ancestral gestational stress may have a role in promoting transgenerational preterm birth risk.[32] Stress can induce the transgenerational inheritance of disease, and ancestral exposures to a variety of factors can alter stress response transgenerationally.

Specific Changes Seen in Transgenerational Epigenetics

- *Reprogramming*: Except for a few loci, most mammalian germlines undergo two rounds of near-complete epigenetic erasure, preimplantation and during primordial germ cell development, making stable transmission difficult;
- *Causality*: True germline epigenetic inheritance needs to be differentiated from environmental/behavioral/social exposure *in utero*/after birth;
- *Reproducibility*: Many transgenerational effects are small, context-dependent, and not consistently replicated across labs/species;

- *Tissue specificity*: Epigenetic marks are often specific for cell-types but not for tissues, as these may show variable composition in terms of germline or target tissues; and
- *Mechanistic proof*: Showing specific epigenetic marks in germ cells that can explain the phenotype(s) in unexposed descendants.

Methods Used to Study Transgenerational Epigenetics

- Animal multi-generation studies with cross-fostering/embryo transfer to control postnatal effects;
- Germline profiling in spermatozoa/eggs using small RNA-seq, bisulfite sequencing for DNA methylation, and ChIP-seq for retained histones;
- Functional tests such as microinjection of altered spermatozoa RNAs into zygotes, CRISPR (clustered regularly interspaced short palindromic repeats)-based epigenome editing to mimic/reverse marks, *in vitro* fertilization, and offspring phenotyping; and
- Epidemiological cohort studies with carefully controlled data about clinical variables and molecular biomarkers.

Clonal Genetic Heterogeneity and Genetic Confounders

Clonal heterogeneity highlights genetic, epigenetic, and/or phenotypic differences between cellular subpopulations.[73–77] In cellular cohorts from various tissues, genetic differences may arise over time due to spontaneous mutations and mitotic recombination.[78,79] Genetic drift may also lead to diversification of cellular variants that adapt to selection pressures.[80]

Generational Toxicology

Exposure to toxins early during development can induce epigenetic changes in germ cells and manifest with genetic/clinical features even in non-exposed future generations; this has led to the development of a new branch of science, generational toxicology. Understanding the role of environmental factors in transgenerational epigenetic inheritance has provided evidence for the inheritance of epimutations and phenotype changes. These epigenetic changes become imprinted in embryonic stem cells and begin to alter cell types throughout life.

There is some evidence that generational toxicity can also alter epigenetic transgenerational inheritance of increased susceptibility to disease. There is a need for focused studies to understand the implications of these exposures. A new approach that takes into consideration generational toxicology will be needed to protect our future populations.

Conclusions

Transgenerational epigenetics represents a rapidly evolving field that challenges traditional views of inheritance by suggesting that environmentally induced epigenetic information can persist beyond direct exposure and influence phenotypes across generations. There is evidence from population studies and animal models about the potential for germline transmission of epigenetic marks. However, there are some confounding data from host factors such as ethnicity, severity of illness, and gender, and concurrent infections that limit our ability to draw robust conclusions about intergenerational effects and environmental continuity. Distinguishing true germline-dependent inheritance from context-dependent somatic effects is therefore crucial. We need well-designed, multi-generational human and experimental animal studies, with integrative molecular analyses to establish causality and mechanisms. Clarifying the extent and stability of transgenerational epigenetic inheritance may help in understanding disease risk, evolutionary biology, and designing public health interventions.

References

1. Crews D, Gore AC. Chapter 26 – Transgenerational Epigenetics: Current Controversies and Debates. In: Tollefsbol T, editor. Transgenerational Epigenetics. Cambridge, Massachusetts: Academic Press; 2014. p. 371–390.
2. Waddington CH. Canalization of development and genetic assimilation of acquired characters. Nature 1959;183(4676):1654–1655. DOI: 10.1038/1831654A0.
3. Costello KR, Schones DE. Chromatin modifications in metabolic disease: Potential mediators of long-term disease risk. Wiley Interdiscip Rev Syst Biol Med. 2018;10(4):e1416. DOI: 10.1002/WSBM.1416.
4. Youngson NA, Whitelaw E. Transgenerational epigenetic effects. Annu Rev Genomics Hum Genet 2008;9:233–257. DOI: 10.1146/ANNUREV.GENOM.9.081307.164445.
5. Crews D, McLachlan JA. Epigenetics, evolution, endocrine disruption, health, and disease. Endocrinology. 2006;147(6 Suppl):S4–S10. DOI: 10.1210/EN.2005-1122.
6. Gilbert SF, Epel D. Integrating epigenetics, medicine, and evolution. Callen H, editor. Sunderland, Massachusetts, United States: Sinauer, Oxford University Press; 2009. p. 1–300.
7. Goldschmidt RB. The Material Basis of Evolution. McInnis M, editor. New Haven, Connecticut, USA: Yale University Press; 1982. p. 1–438.
8. Waddington CH. Epigenetics: A Treatise on Theoretical Biology. By Søren Løvtrup. John Wiley and Sons, London, 1974. p. ix+547. £15.00. Q J Exp Physiol Cogn Med Sci 1974;59(3):261–262. DOI: 10.1113/EXPPHYSIOL.1974.SP002270.
9. Crews D, Gore AC. Epigenetic synthesis: A need for a new paradigm for evolution in a contaminated world. F1000 Biol Rep 2012;4(1):18. DOI: 10.3410/B4-18.
10. Gore AC. Developmental programming and endocrine disruptor effects on reproductive neuroendocrine systems. Front Neuroendocrinol 2008;29(3):358–374. DOI: 10.1016/J.YFRNE.2008.02.002.
11. Crews D. Epigenetic modifications of brain and behavior: Theory and practice. Horm Behav 2011;59(3):393–398. DOI: 10.1016/J.YHBEH.2010.07.001.
12. Crews D. Epigenetics and its implications for behavioral neuroendocrinology. Front Neuroendocrinol 2008;29(3):344–357. DOI: 10.1016/J.YFRNE.2008.01.003.
13. Reik W, Dean W, Walter J. Epigenetic reprogramming in mammalian development. Science 2001;293(5532):1089–1093. DOI: 10.1126/SCIENCE.1063443.
14. Almouzni G, Altucci L, Amati B, et al. Relationship between genome and epigenome - challenges and requirements for future research. BMC Genomics 2014;15(1):1–7. DOI: 10.1186/1471-2164-15-487/FIGURES/1.
15. Lister R, Pelizzola M, Dowen RH, et al. Human DNA methylomes at base resolution show widespread epigenomic differences. Nature 2009;462(7271):315–322. DOI: 10.1038/NATURE08514.
16. Khatib H, Townsend J, Konkel MA, et al. Calling the question: What is mammalian transgenerational epigenetic inheritance? Epigenetics. 2024;19(1):2333586. DOI: 10.1080/15592294.2024.2333586.
17. Fitz-James MH, Cavalli G. Molecular mechanisms of transgenerational epigenetic inheritance. Nat Rev Genet 2022;23(6):325–341. DOI: 10.1038/S41576-021-00438-5.

18. Rea S, Eisenhaber F, O'Carroll D, et al. Regulation of chromatin structure by site-specific histone H3 methyltransferases. Nature 2000;406(6796):593–599. DOI: 10.1038/35020506.
19. Klose RJ, Kallin EM, Zhang Y. JmjC-domain-containing proteins and histone demethylation. Nat Rev Genet 2006;7(9):715–727. DOI: 10.1038/NRG1945.
20. Galdieri L, Vancura A. Acetyl-CoA carboxylase regulates global histone acetylation. J Biol Chem 2012;287(28):23865–23876. DOI: 10.1074/JBC.M112.380519.
21. Moelling K. Epigenetics and transgenerational inheritance. J Physiol 2024;602(11):2537–2545. DOI: 10.1113/JP284424.
22. Schulz LC. The Dutch Hunger Winter and the developmental origins of health and disease. Proc Natl Acad Sci USA 2010;107(39):16757–16758. DOI: 10.1073/PNAS.1012911107.
23. Ahima RS. Connecting obesity, aging and diabetes. Nat Med 2009;15(9):996–997. DOI: 10.1038/NM0909-996.
24. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol 2013;14(10):R115. DOI: 10.1186/GB-2013-14-10-R115.
25. Stubbs TM, Bonder MJ, Stark AK, et al. Multi-tissue DNA methylation age predictor in mouse. Genome Biol. 2017;18(1):68. DOI: 10.1186/S13059-017-1203-5.
26. Wang T, Tsui B, Kreisberg JF, et al. Epigenetic aging signatures in mice livers are slowed by dwarfism, calorie restriction and rapamycin treatment. Genome Biol. 2017;18(1):57. DOI: 10.1186/S13059-017-1186-2.
27. Cole JJ, Robertson NA, Rather MI, et al. Diverse interventions that extend mouse lifespan suppress shared age-associated epigenetic changes at critical gene regulatory regions. Genome Biol 2017;18(1):58. DOI: 10.1186/S13059-017-1185-3.
28. Stouder C, Paoloni-Giacobino A. Transgenerational effects of the endocrine disruptor vinclozolin on the methylation pattern of imprinted genes in the mouse sperm. Reproduction 2010;139(2):373–379. DOI: 10.1530/REP-09-0340.
29. Guerrero-Bosagna C, Settles M, Lucker B, et al. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. PLoS One 2010;5(9):e13100. DOI: 10.1371/JOURNAL.PONE.0013100.
30. Vandegehuchte MB, Lemière F, Vanhaecke L, et al. Direct and transgenerational impact on Daphnia magna of chemicals with a known effect on DNA methylation. Comp Biochem Physiol C Toxicol Pharmacol 2010;151(3):278–285. DOI: 10.1016/J.CBPC.2009.11.007.
31. Schneider S, Marxfeld H, Gröters S, et al. Vinclozolin—No transgenerational inheritance of anti-androgenic effects after maternal exposure during organogenesis via the intraperitoneal route. Reprod Toxicol 2013;37:6–14. DOI: 10.1016/J.REPROTOX.2012.12.003.
32. Nilsson E, Larsen G, Manikkam M, et al. Environmentally induced epigenetic transgenerational inheritance of ovarian disease. PLoS One 2012;7(5):e36129. DOI: 10.1371/JOURNAL.PONE.0036129.
33. Inawaka K, Kawabe M, Takahashi S, et al. Maternal exposure to anti-androgenic compounds, vinclozolin, flutamide and procymidone, has no effects on spermatogenesis and DNA methylation in male rats of subsequent generations. Toxicol Appl Pharmacol 2009;237(2):178–187. DOI: 10.1016/J.TAAP.2009.03.004.
34. Guerrero-Bosagna C, Covert TR, Haque MM, et al. Epigenetic transgenerational inheritance of vinclozolin induced mouse adult onset disease and associated sperm epigenome biomarkers. Reprod Toxicol 2012;34(4):694–707. DOI: 10.1016/J.REPROTOX.2012.09.005.
35. Crews D, Gillette R, Scarpino SV, et al. Epigenetic transgenerational inheritance of altered stress responses. Proc Natl Acad Sci USA 2012;109(23):9143–9148. DOI: 10.1073/PNAS.1118514109/SUPPL_FILE/SD01.PDF.
36. Nilsson EE, Anway MD, Stanfield J, et al. Transgenerational epigenetic effects of the endocrine disruptor vinclozolin on pregnancies and female adult onset disease. Reproduction 2008;135(5):713–721. DOI: 10.1530/REP-07-0542.
37. Crews D, Gore AC, Hsu TS, et al. Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci USA 2007;104(14):5942–5946. DOI: 10.1073/PNAS.0610410104/SUPPL_FILE/10410MOVIE1.AVI.
38. Newbold RR, Padilla-Banks E, Jefferson WN. Adverse effects of the model environmental estrogen diethylstilbestrol are transmitted to subsequent generations. Endocrinology. 2006;147(6 Suppl):S11–S17. DOI: 10.1210/EN.2005-1164.
39. Kalfa N, Paris F, Soyer-Gobillard MO, et al. Prevalence of hypospadias in grandsons of women exposed to diethylstilbestrol during pregnancy: A multigenerational national cohort study. Fertil Steril 2011;95(8):2574–2577. DOI: 10.1016/J.FERTNSTERT.2011.02.047.
40. Rubin MM. Antenatal exposure to DES: Lessons learned ... future concerns. Obstet Gynecol Surv 2007;62(8):548–555. DOI: 10.1097/01.OGX.0000271138.31234.D7.
41. Storgaard L, Bonde JP, Olsen J. Male reproductive disorders in humans and prenatal indicators of estrogen exposure: A review of published epidemiological studies. Reprod Toxicol 2006;21(1):4–15. DOI: 10.1016/J.REPROTOX.2005.05.006.
42. Bošković A, Rando OJ. Transgenerational epigenetic inheritance. Annu Rev Genet 2018;52(Volume 52, 2018):21–41. DOI: 10.1146/ANNUREV-GENET-120417-031404/CITE/REFWORKS.
43. Rosenfeld CS. Chapter 11 – Animal Models of Transgenerational Epigenetic Effects. In: Transgenerational Epigenetics. Cambridge, Massachusetts, USA: Academic Press; 2014. p. 123–145.
44. Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. Horm Behav 2011;59(3):290–295. DOI: 10.1016/J.YHBEH.2010.05.004.
45. Zhang T, Dwight R. Choosing an optimal model for failure data analysis by graphical approach. Reliab Eng Syst Saf 2013;115:111–123. DOI: 10.1016/J.RESS.2013.02.004.
46. Bagot RC, Tse YC, Nguyen HB, et al. Maternal care influences hippocampal N-methyl-D-aspartate receptor function and dynamic regulation by corticosterone in adulthood. Biol Psychiatry 2012;72(6):491–498. DOI: 10.1016/J.BIOPSYCH.2012.03.016.
47. Daxinger L, Whitelaw E. Understanding transgenerational epigenetic inheritance via the gametes in mammals. Nature Rev Genetics 2012;13(3):153–162. DOI: 10.1038/nrg3188.
48. Jensen P. Transgenerational epigenetic effects on animal behaviour. Prog Biophys Mol Biol 2013;113(3):447–454. DOI: 10.1016/J.PBIOMOLBIO.2013.01.001.
49. Wolff GL, Kodell RL, Moore SR, et al. Maternal epigenetics and methyl supplements affect agouti gene expression in Avy/a mice. FASEB J 1998;12(11):949–957. DOI: 10.1096/FASEBJ.12.11.949.
50. Cooney CA, Dave AA, Wolff GL. Maternal methyl supplements in mice affect epigenetic variation and DNA methylation of offspring. J Nutr 2002;132(8):2393S–2400S. DOI: 10.1093/JN/132.8.2393S.
51. Wolff GL, Medina D, Umholtz RL. Manifestation of hyperplastic alveolar nodules and mammary tumors in "Viable Yellow" and non-yellow mice. JNCI: J Natl Cancer Institute 1979;63(3):781–785. DOI: 10.1093/JNCI/63.3.781.
52. Wolff GL, Roberts DW, Galbraith DB. Prenatal determination of obesity, tumor susceptibility, and coat color pattern in viable yellow (Avy/a) mice: The yellow mouse syndrome. J Hered 1986;77(3):151–158. DOI: 10.1093/OXFORDJOURNALS.JHERED.A110206.
53. Wolff GL, Roberts DW, Morrissey RL, et al. Tumorigenic responses to lindane in mice: potentiation by a dominant mutation. Carcinogenesis 1987;8(12):1889–1897. DOI: 10.1093/CARCIN/8.12.1889.
54. Wolff GL, Roberts DW, Mountjoy KG. Physiological consequences of ectopic agouti gene expression: The yellow obese mouse syndrome. Physiol Genomics 1999;1999(1):151–163. DOI: 10.1152/PHYSIOLGENOMICS.1999.1.3.151/ASSET/IMAGES/LARGE/PHYS65805001BX.JPEG.
55. Rosenfeld CS. Animal models to study environmental epigenetics. Biol Reprod 2010;82(3):473–488. DOI: 10.1095/BIOLREPROD.109.080952.
56. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet 2007;8(4):253. DOI: 10.1038/NRG2045.

57. Lillycrop KA. Effect of maternal diet on the epigenome: Implications for human metabolic disease. Proc Nutr Soc 2011;70(1):64–72. DOI: 10.1017/S0029665110004027.
58. Godfrey KM, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 2011;60(5):1528–1534. DOI: 10.2337/DB10-0979.
59. Weaver ICG. Shaping adult phenotypes through early life environments. Birth Defects Res C Embryo Today 2009;87(4):314–326. DOI: 10.1002/BDRC.20164.
60. Lu D, Willard D, Patel IR, et al. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. Nature 1994;371(6500):799–802. DOI: 10.1038/371799A0.
61. Smith SR, Gawronska-Kozak B, Janderová L, et al. Agouti expression in human adipose tissuefunctional consequences and increased expression in type 2 diabetes. Diabetes 2003;52(12):2914–2922. DOI: 10.2337/DIABETES.52.12.2914.
62. Xue BZ, Wilkison WO, Mynatt RL, et al. The agouti gene product stimulates pancreatic β-cell Ca2+ signaling and insulin release. Physiol Genomics 1999;1999(1):11–19. DOI: 10.1152/PHYSIOLGENOMICS.1999.1.1.11/ASSET/IMAGES/LARGE/PHYS65603006W.JPEG.
63. Mynatt RL, Stephens JM. Agouti regulates adipocyte transcription factors. Am J Physiol Cell Physiol 2001;280(4):C954–C961. DOI: 10.1152/AJPCELL.2001.280.4.C954.
64. Voisey J, Van Daal A. Agouti: From mouse to man, from skin to fat. Pigment Cell Res 2002;15(1):10–18. DOI: 10.1034/J.1600-0749.2002.00039.X.
65. Norman RA, Tataranni PA, Pratley R, et al. Autosomal genomic scan for loci linked to obesity and energy metabolism in Pima Indians. Am J Human Genetics 1998;62(3):659–668. DOI: 10.1086/301758.
66. Blewitt ME, Vickaryous NK, Paldi A, et al. Dynamic reprogramming of DNA methylation at an epigenetically sensitive allele in mice. PLoS Genet 2006;2(4):e49. DOI: 10.1371/JOURNAL.PGEN.0020049.
67. Rakyan VK, Blewitt ME, Druker R, et al. Metastable epialleles in mammals. Trends Genetics 2002;18(7):348–351. DOI: 10.1016/S0168-9525(02)02709-9.
68. Dolinoy DC, Das R, Weidman JR, et al. Metastable epialleles, imprinting, and the fetal origins of adult diseases. Pediatr Res 2007;61(7):30–37. DOI: 10.1203/pdr.0b013e31804575f7.
69. Arteaga-Vazquez MA, Chandler VL. Paramutation in maize: RNA mediated trans-generational gene silencing. Curr Opin Genet Dev 2010;20(2):156. DOI: 10.1016/J.GDE.2010.01.008.
70. Lacal I, Ventura R. Epigenetic Inheritance: Concepts, Mechanisms and Perspectives. Front Mol Neurosci 2018;11:292. DOI: 10.3389/FNMOL.2018.00292.
71. Van Otterdijk SD, Michels KB. Transgenerational epigenetic inheritance in mammals: How good is the evidence? FASEB J 2016;30(7):2457–2465. DOI: 10.1096/FJ.201500083.
72. Bennett-Baker PE, Wilkowski J, Burke DT. Age-associated activation of epigenetically repressed genes in the mouse. Genetics 2003;165(4):2055–2062. DOI: 10.1093/GENETICS/165.4.2055.
73. Kuijk E, Jager M, van der Roest B, et al. The mutational impact of culturing human pluripotent and adult stem cells. Nat Commun 2020;11(1):2493. DOI: 10.1038/S41467-020-16323-4.
74. Laurent LC, Ulitsky I, Slavin I, et al. Dynamic changes in the copy number of pluripotency and cell proliferation genes in human ESCs and iPSCs during reprogramming and time in culture. Cell Stem Cell 2011;8(1):106–118. DOI: 10.1016/j.stem.2010.12.003.
75. Kwon EM, Connelly JP, Hansen NF, et al. iPSCs and fibroblast subclones from the same fibroblast population contain comparable levels of sequence variations. Proc Natl Acad Sci USA 2017;114(8):1964–1969. DOI: 10.1073/PNAS.1616035114.
76. Ben-David U, Mayshar Y, Benvenisty N. Large-scale analysis reveals acquisition of lineage-specific chromosomal aberrations in human adult stem cells. Cell Stem Cell 2011;9(2):97–102. DOI: 10.1016/j.stem.2011.06.013.
77. Taapken SM, Nisler BS, Newton MA, et al. Karotypic abnormalities in human induced pluripotent stem cells and embryonic stem cells. Nat Biotechnol 2011;29(4):313–314. DOI: 10.1038/NBT.1835.
78. Ben-David U, Siranosian B, Ha G, et al. Genetic and transcriptional evolution alters cancer cell line drug response. Nature 2018;560(7718):325–330. DOI: 10.1038/S41586-018-0409-3.
79. Quevedo R, Smirnov P, Tkachuk D, et al. Assessment of genetic drift in large pharmacogenomic studies. Cell Syst 2020;11(4):393–401.e2. DOI: 10.1016/j.cels.2020.08.012.
80. Sapozhnikov DM, Szyf M. Genetic confounds of transgenerational epigenetic inheritance in mice. Epigenetics. 2024;19(1):2318519. DOI: 10.1080/15592294.2024.2318519.

PICTORIAL ESSAY

Systemized Systemic Sono-screening (S4) Protocol: Initial Findings

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Abstract

We are developing a systemized protocol for major-system sonographic screening, an extended physical examination in critically ill infants. This program includes a brief examination of the brain, heart, lungs, intestine, and genitals. We also check the central line catheters for correct positioning and complications such as thrombi. This protocol gives more information than the traditional point-of-care ultrasound (POCUS) developed over the past two decades. In our recent screening of medical records, we have noted a high incidence of intracardiac thrombi in the right cardiac chambers. Some of these thrombi could well result from the longer durations for which umbilical venous catheters (UVCs) were used, but not every patient had undergone umbilical venous catheterization. The perception of lower blood flow velocities on the right side as a causative factor may also not be entirely correct; the hemodynamic measurements may vary at specific location(s) within the vessels/chambers, at various time-points in the cardiac cycle, and with physiological conditions such as ventricular hypertrophy. The high frequency of clots in the right heart chambers needs evaluation in larger, carefully designed studies.

Keywords: Echocardiography, Infant, Intra-cardiac thrombi, Neonate, Newborn, Point-of-care ultrasound, Sonographic screening, Subcostal views, Umbilical arterial catheters, Umbilical venous catheters.

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Key Points

- We are developing a systemized protocol for major-system sonographic screening, an extended physical examination in critically ill infants.
- Our initial records of sonographic examinations show a high frequency of intra-cardiac thrombi, particularly on the right side.
- Umbilical venous catheters (UVCs) may be as or more frequently associated with thrombi than with umbilical arterial catheters.
- The higher incidence of thrombi in the right heart could be explained in some infants based on the length of time for which UVCs were used, but not all of these patients had a history of umbilical venous catheterization. The perception of lower blood flow velocities on the right side as a causative factor may also not be entirely correct. Our findings need evaluation in larger, carefully designed studies.

Introduction

We are developing a systemized protocol for major-system sonographic screening, an extended physical examination in critically ill infants. This program includes a brief examination of the brain, heart, lungs, intestine, and genitals. We also check the central line catheters for correct positioning and complications such as thrombi. These steps provide more information than the traditional point-of-care ultrasound (POCUS) protocols developed over the past two decades.

In this pictorial essay, we have shown some intra-cardiac thrombi. Close analysis of our sonographic records has shown a high frequency of these clots on the right side of the heart.[1–3] In our neonatal intensive care units, we typically use UVCs for 7–10 days after birth but have removed umbilical arterial catheters

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(UACs) sooner, as early as 3–5 days. Many clots were seen right on the tip of the UVC (Fig. 1A), but others were attached to the tricuspid valve (Fig. 1B) or to the right atrium (RA) septum (Fig. 1C). Some of these patients did not have a history of umbilical venous catheterization.

These findings need evaluation in larger, carefully designed studies. Our records clearly suggest that UVCs may not necessarily be more benign than UACs. Hence, the need for a UVC in an infant should be closely monitored, and it should be removed immediately if not needed. However, other factors may also be at play; many clots were seen in infants who had not undergone umbilical venous catheterization. The perception of lower blood flow velocities on the right side as a causative factor may also not be entirely correct. The measured values may vary at specific location(s) within the vessels/chambers, at various time-points in the cardiac cycle, and with physiological conditions such as ventricular hypertrophy. The left ventricle (LV) has a thicker wall as it operates under higher pressures and pumps blood to the entire body, and the blood flow velocities can be high. In contrast, the inferior vena cava (IVC) has a larger diameter and returns blood to the RA with varying blood flow velocities depending on the respiratory pressure gradients. There is a need for more information.

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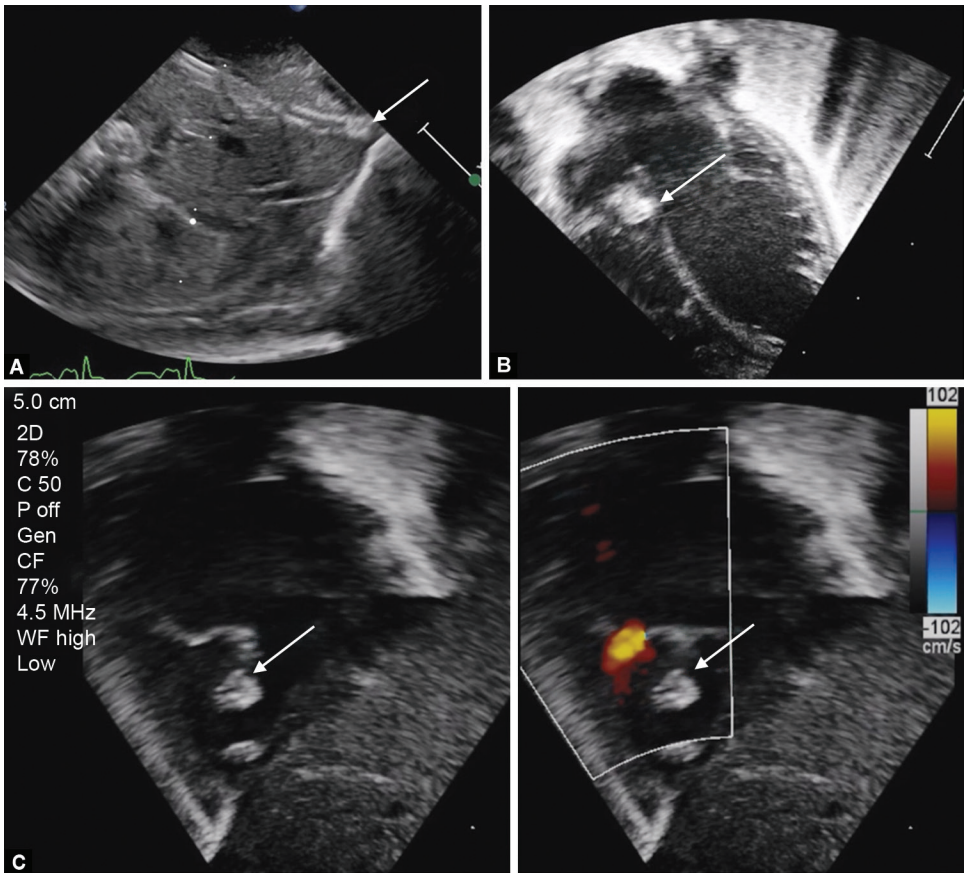
Conflict of interest: Dr Akhil Maheshwari is associated as the Editor-in-Chief of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of Editor-in-Chief and his research group.



Figs 1A to C: (A) A thrombus seen as an echodense intraluminal mass (arrow) at the UVC tip at the IVC-RA junction. Subcostal views (longitudinal) are useful for these evaluations; (B) A clot seen attached to the tricuspid valve (arrow) in apical four-chamber and/or subcostal bi-caval views; (C) A thrombus seen on the RA septum (interatrial region; arrow). These can be seen more frequently in the presence of a patent foramen ovale (PFO; Doppler view on the right image). A subcostal four-chamber view can be optimal for imaging the atrial septum in neonates. Parasternal long-axis and short-axis views can also be useful

References

1. Sobczak A, Dudzik A, Kruczek P, et al. Ultrasound monitoring of umbilical catheters in the neonatal intensive care unit – A prospective

observational study. Front Pediatr 2021;9:665214. DOI: 10.3389/fped.2021.665214.
2. Farag MM, Ghazal HAR, Radwan MM, et al. Catheters linked thrombosis in neonates: A single center observational study. Ital J Pediatr 2024;50:147. DOI: 10.1186/s13052-024-01708-8.
3. De Rose DU, Mecarini F, Campanale CM, et al. Management of intracardiac thrombosis in newborns: A case series and a narrative review of the literature. Front Cardiovasc Med 2025;12:1659312. DOI: 10.3389/fcvm.2025.1659312.

PICTORIAL ESSAY

Clinical Illustration: Autosomal Recessive Polycystic Kidney Disease

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Abstract

This article presents illustrative images suggestive of autosomal recessive polycystic kidney disease (ARPKD) from a young child born at full-term gestational age. She had a prior history of repeated episodes of fevers, and during her systemic evaluation, she was noted to have abnormal plasma renal function indices. Renal ultrasound showed enlarged kidneys with increased echogenicity, multiple cysts of varying sizes, and loss of normal corticomedullary differentiation. Sonographic images of the liver showed two anechoic cystic areas, possibly representing a combination of von Meyenburg complexes (biliary hamartomas) and focal intrahepatic biliary dilation, indicating Caroli disease.

Keywords: Autosomal recessive polycystic kidney disease, Biliary hamartomas, Caroli disease, Caroli syndrome, Congenital hepatic fibrosis, Focal intrahepatic biliary dilation, Infant, Oligohydramnios, Polycystic kidney and hepatic disease 1, Renal tubular ectasia, von Meyenburg complexes.

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Key Points

- Autosomal recessive polycystic kidney disease (ARPKD) is a hereditary renal cystic disorder, most frequently associated with mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene on chromosome 6p12.
- We present sonographic images of both kidneys and the liver in a young child showing changes characteristic of ARPKD and Caroli disease.
- Careful assessment can help diagnose the condition *in utero* in mothers presenting with oligohydramnios resulting from low fetal urine production and characteristic sonographic changes in the fetal kidneys.

Clinical History

A 30-month-old female born at full-term gestational age was seen in her first clinical visit following immigration into the United States. She had a prior history of repeated episodes of fevers. Antenatal history was not available. She was evaluated by a kidney ultrasound in view of abnormal plasma renal function indices.

Discussion

Autosomal recessive polycystic kidney disease is a rare inherited childhood condition where the development of the kidneys and liver is abnormal.[1–4] More than 90% of cases have mutations in the PKHD1 gene on chromosome 6p12.[5] Polycystic kidney and hepatic disease 1 promotes the expression of the fibrocystin protein, which is involved in cellular adhesion, ciliary function, and cell proliferation in the kidney and liver.[6–8] There is evidence of extensive alternative splicing of this gene; a critical amount of full-length protein is needed for tubular epithelial function. A few

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patients show mutations in the DAZ (Deleted in Azoospermia)-interacting zinc finger protein 1-like (DZIP1L), which is involved in primary cilium assembly (Figs 1 to 3).[9]

The condition is characterized by ectasia and cystic dilation of the renal tubules.[1–4] It is increasingly being diagnosed in *in utero* due to oligohydramnios resulting from low urine production by the affected kidneys. After birth, an ultrasound may show both kidneys as enlarged, multiple small cysts with echogenic membranes in each, and loss of corticomedullary differentiation on both sides. Liver involvement can present with cysts/biliary hamartomas (von Meyenburg complexes), focal cystic dilation of the intrahepatic bile ducts (Caroli disease), and congenital hepatic fibrosis (Caroli syndrome). These changes may manifest with portal hypertension.[1,2]

There is a need for clinicians to consider this condition in the differential diagnosis of infants with renal dysfunction. Autosomal recessive polycystic kidney disease is one of the most common causes of heritable, infantile cystic renal disease. In non-isolated populations, the carrier frequency may be up to 1 in 70.[9] However,

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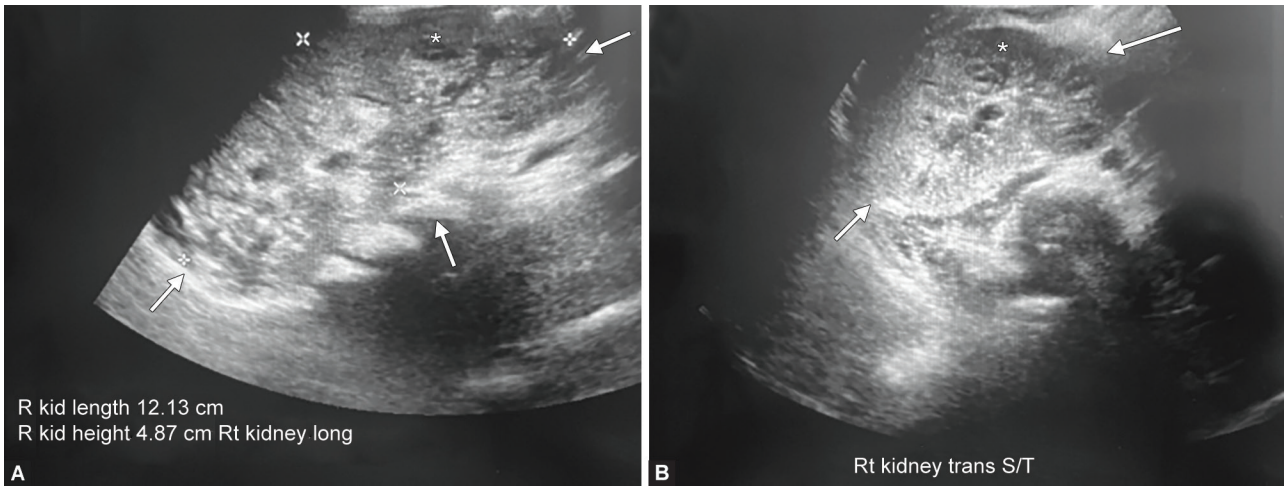
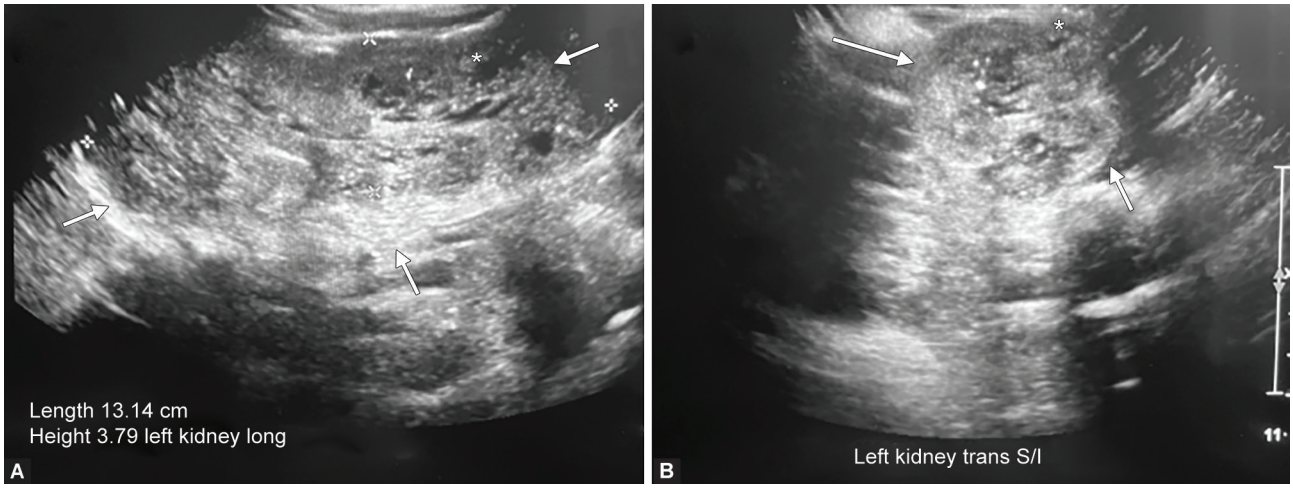
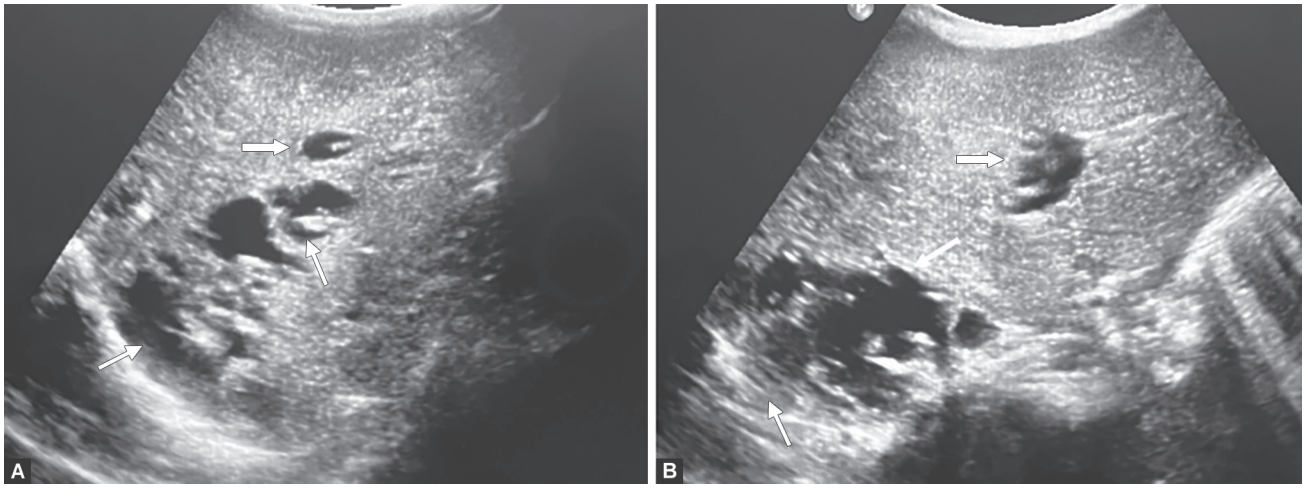


Figs 1A and B: (A) Longitudinal; and (B) Transverse sonographic images of the right kidney (arrows) showing an enlarged kidney (for her age; arrows) with increased echogenicity, multiple cysts of varying sizes (*), and loss of normal corticomedullary differentiation. These findings were consistent with ARPKD



Figs 2A and B: (A) Longitudinal; and (B) Transverse sonographic images from the same patient of the left kidney showing enlarged left kidneys (arrows) with increased echogenicity, multiple small cysts (*), and loss of normal corticomedullary differentiation



Figs 3A and B: (A and B) Sonographic images of the right lobe of the liver showing a cluster of anechoic cystic areas peripherally (small white arrows), probably representing biliary hamartomas (von Meyenburg complexes), and small irregular cystic areas (thick arrows) representing focal intrahepatic biliary dilation (Caroli disease) associated with ARPKD

the disease is being diagnosed in a timely fashion in only 1 in 20,000–40,000 live births.[3] More efforts are needed.

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References

1. Dillman JR, Trout AT, Smith EA, et al. Hereditary renal cystic disorders: Imaging of the kidneys and beyond. Radiographics 2017;37(3):924–946. DOI: 10.1148/rg.2017160148.
2. Simmons CL, Harper LK, Patel MC, et al. Biliary disorders, anomalies, and malignancies in children. Radiographics 2024;44(3):e230109. DOI: 10.1148/rg.230109.
3. Traubici J, Daneman A. High-resolution renal sonography in children with autosomal recessive polycystic kidney disease. AJR Am J Roentgenol 2005;184(5):1630–1633. DOI: 10.2214/ajr.184.5.01841630.
4. Bergmann C, Guay-Woodford LM, Harris PC, et al. Polycystic kidney disease. Nat Rev Dis 2018;4(1):50. DOI: 10.1038/s41572-018-0047-y.
5. Bergmann C, Senderek J, Küpper F, et al. PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat 2004;23(5):453–463. DOI: 10.1002/humu.20029.
6. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet 2002;30(3):259–269. DOI: 10.1038/ng833.
7. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. Am J Hum Genet 2002;70(5):1305–1317. DOI: 10.1086/340448.
8. Menezes LFC, Cai Y, Nagasawa Y, et al. Polyductin, the PKHD1 gene product, comprises isoforms expressed in plasma membrane, primary cilium, and cytoplasm. Kidney Int 2004;66(4):1345–1355. DOI: 10.1111/j.1523-1755.2004.00844.x.
9. Liebau MC. Early clinical management of autosomal recessive polycystic kidney disease. Pediatr Nephrol 2021;36(11):3561–3570. DOI: 10.1007/s00467-021-04970-8.