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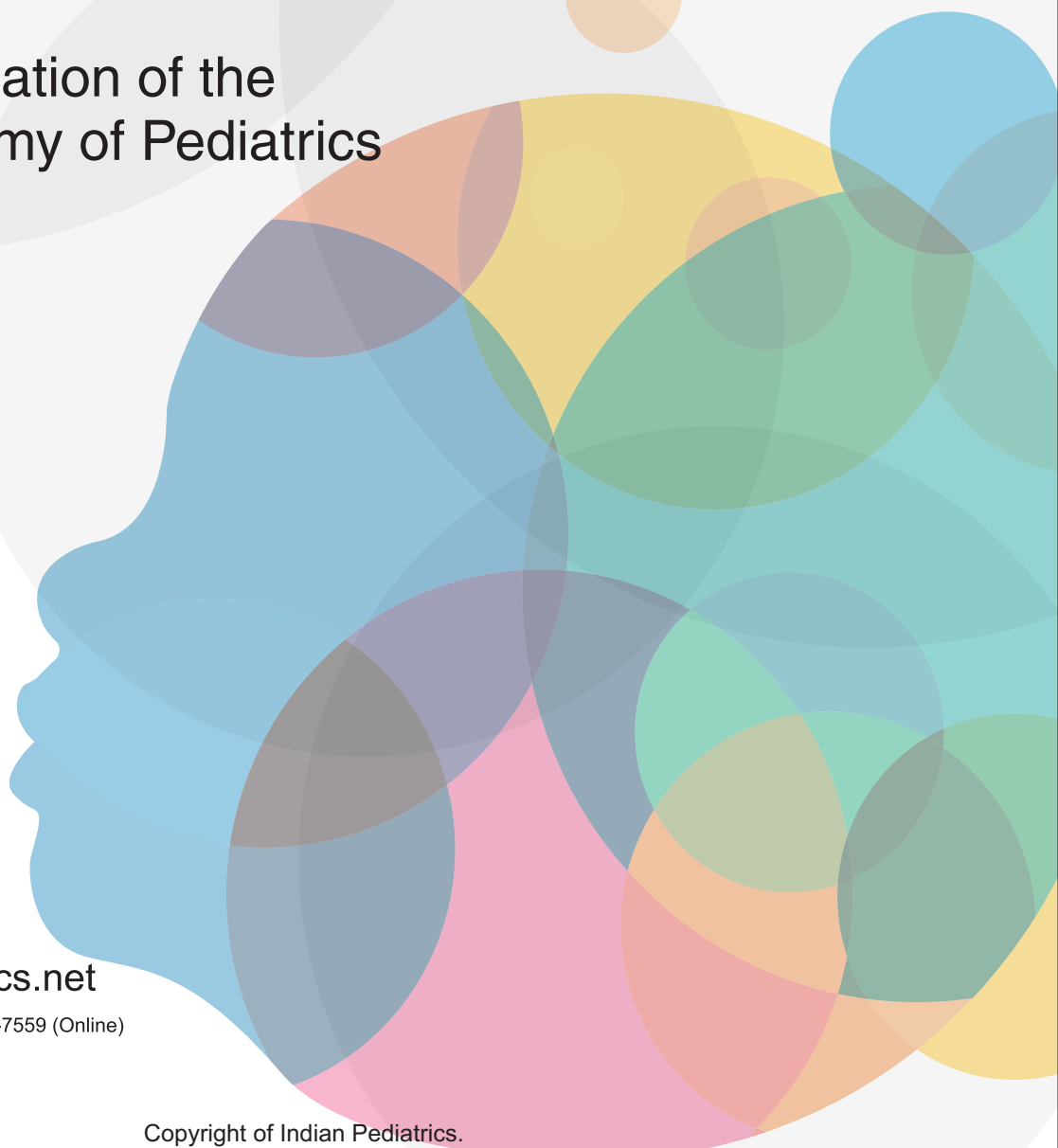

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PRESIDENT'S PAGE

Embracing Differences: Raising Awareness About Autism Spectrum Disorder and Down Syndrome

GV Basavaraja

National President, Indian Academy of Pediatrics, 2024
president@iapindia.org

Dear Esteemed Members of the *Indian Academy of Pediatrics* (IAP),

As we step into April and celebrate the '*Autism Awareness Month*', I wish to draw your attention to this enigma called '*Autism Spectrum Disorder (ASD)'* which demands our collective understanding and action. Studies have shown a staggering increase in the prevalence of ASD from 1 in every 2000 individuals to a concerning 1% more recently [1-3]. The rise in the incidence of ASD has been attributed to a multitude of factors including genetic and non-genetic elements like advancing age of parents, maternal obesity, alcohol consumption during pregnancy, use of antiepileptic drugs by the mother, perinatal insult to the fetus [4], in addition to an increased recognition of the condition due to improved awareness within the medical fraternity as well as society [5].

Early diagnosis and intervention are of paramount importance in addressing the challenges posed by ASD. Research strongly demonstrates that timely identification and appropriate interventions significantly improve long-term outcomes, mitigating symptoms and fostering the development of crucial skills [6]. In fact, ASD can often be identified in children before they reach the age of 2, and some children, whose development appeared typical, may experience regression around this critical period.

A plethora of screening tools, such as the Childhood Autism Rating Scale, Second Edition (CARS-2), Autism Spectrum Screening Questionnaire (ASSQ), Modified Checklist for Autism in Toddlers (M-CHAT), and Pervasive Developmental Disorder Screening Test-2 (PDDST-2), are now readily available for clinicians. These tools enable early detection and intervention, providing a beacon of hope for a brighter future for affected children. With minimal additional time required in routine clinical practice, we can strive for better outcomes for our children.

Educational strategies, such as the renowned Treatment and Education of Autistic and Communication Handicapped Children (TEACCH), offer structured teaching methodologies, utilize visual supports, and tailor environments to meet the unique needs of individuals with ASD. These interventions have shown remarkable efficacy in enhancing cognitive and adaptive skills, empowering individuals to navigate the world more confidently.

Amidst our efforts to diagnose and treat ASD, we must confront and dispel the myths that shroud this condition. Misinformation regarding vaccinations, contagiousness, or even parental abuse only serves to perpetuate the stigma and hinder progress. It is incumbent upon us to disseminate accurate information, debunk myths, and foster a culture of understanding and acceptance within our communities. On this World Autism Day on 2nd April, let us pledge to spread the right knowledge and increase awareness about ASD.

As we close on March, a month when we celebrated the Down Syndrome Day on 21 March, let us remember to fulfil our duty as responsible health professionals to help make public attitudes more accepting of *Down Syndrome*. The prevalence of Down Syndrome underscores the importance of community awareness and support. Through this campaign, we aim to eliminate the unfounded social stigmas that surround this condition.

As pediatricians, we shoulder the dual responsibility of both early diagnosis and prevention of Down syndrome, a genetic condition affecting approximately 1 in 650 to 1000 live births [7]. Our first task lies in the meticulous screening for various abnormalities associated with Down Syndrome, ensuring timely detection and intervention. This involves a comprehensive approach encompassing regular follow-up and screening for hypothyroidism, Hirschsprung's disease, leukemia, hearing impairments, ophthalmological issues, and developmental delay at the time of diagnosis and throughout the child's development.

Beyond diagnosis, our role extends to empowering the parents with knowledge and support. We must engage in open and empathetic communication, educating families about the condition and provide information about the available resources for the effective management. It is crucial to dispel misconceptions, alleviate fears, and reassure parents that while Down Syndrome presents unique challenges, it is a manageable condition. By emphasizing the potential for a fulfilling life with proper care and access to resources such as occupational therapy, we can instill hope and confidence in families facing this diagnosis.

As advocates for preventive healthcare, we advocate for prenatal screening and equipping prospective parents with the information they need to make informed decisions about pregnancy. By facilitating discussions about prenatal testing options and the implications of a positive diagnosis, we empower individuals to take proactive steps in their reproductive health journey.

In our commitment to comprehensive care, we recognize the importance of ongoing support for families navigating the complexities of raising a child with ASD or Down Syndrome. This entails fostering a network of support services, connecting families with community resources, and advocating for inclusive education and social opportunities. Through collaboration with multidisciplinary teams and community organizations, we strive to create a supportive environment where every child, regardless of ability, can thrive and reach their full potential.

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Indian Academy of Pediatrics Consensus Guidelines on Preconception Care

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ABSTRACT

Justification: The preconception period is the earliest window of opportunity to ensure optimal human development. Pregnancy and childbirth outcomes can be improved by interventions offered to support the health and well-being of women and couples prior to conception. Thus, preconception care is essential in preparing for the first thousand days of life. Adolescence, the stage of life that typically comes before the preconception stage, is characterized by various high-risk behaviors like substance abuse, sexual experimentation, injuries, obesity, and mental health issues which can adversely affect their health in adult life. Thus, a Consensus Guideline for pediatricians on providing preconception care to adolescents and young adults can go a long way in making the generations to come, healthier and more productive.

Objective: The purpose of these recommendations is to formulate an evidence-based Consensus Statement that can serve as a guidance for medical professionals to provide preconception care for young adults and adolescents.

Intended Users: All obstetric, pediatric, and adolescent health care providers.

Target Population: Adolescents and young adults.

Process: A large proportion of adolescents seek care from pediatricians and there is a lack of Consensus Guidelines on preconception care. Therefore, the Indian Academy of Pediatrics called an online National Consultative Meeting on April 03, 2023, under the chairmanship of Dr MKC Nair and the National Convenor Dr Himabindu Singh. A group of pediatricians with wide experience and expertise in adolescent health care were assigned the task of formulating evidence-based guidelines on preconception care. The group conducted a comprehensive review of existing evidence by searching resources including PubMed and Cochrane databases. Subsequently, a physical meeting was held at Amritsar on October 07, 2023 during which the consensus was reached through discussions and voting. The level of evidence (LoE) of each recommendation was graded as per the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011.

Recommendations: Every woman planning a pregnancy needs to attain and maintain a eumetabolic state. Prospective couples need to be counselled on the importance of a healthy lifestyle including a nutritious diet, avoidance of substance abuse, and timely screening for genetic disorders. Screening for and management of sexually transmitted diseases in males and females, appropriate vaccination and addressing mental health concerns are also recommended.

Keywords: *Adolescent, Contraception, Eumetabolic, Genetic Screening, Nutrition, Pregnancy, Reproductive Health*

INTRODUCTION

For the health and development of the unborn child, the period prior to conception is vital. Preconception care is the provision of biomedical, behavioral and social health interventions to women and couples before conception occurs to ensure a good pregnancy outcome [1]. Preconception care encompasses several domains, including health promotion, risk assessment, and management of

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pre-existing conditions [2]. Reducing maternal and fetal morbidity and mortality, improving the likelihood of conception when desired, and offering contraceptive counseling to avoid unwanted pregnancies are the main goals of preconception care. It aims to establish a healthy lifestyle and prepare the couple psychologically for pregnancy and parenthood. In recent years, there has been a growing body of evidence demonstrating the significance of preconception care in the prevention of neonatal and birth disorders. According to research, an individual's health and lifestyle choices prior to conception can have a significant impact on the health outcomes of their offspring [3]. Preconception care can reduce the incidence of various neonatal and birth disorders by addressing modifiable risk factors and providing targeted interventions, resulting in healthier pregnancies and better long-term health outcomes for children.

Adverse perinatal events can have long-term consequences for individuals and their families. Neonatal and birth disorders can manifest as physical, cognitive, or developmental abnormalities and can have a significant impact on the well-being and quality of life of affected individuals [4].

According to The United Nations Population Fund (UNFPA), out of 121 million pregnancies worldwide - nearly half are unwanted**.** Over 60% of these unwanted pregnancies end in abortion with an estimated 45% of abortions being unsafe. Abortions also account for 5-13% of all maternal fatalities. This significantly hinders the global efforts to meet the Sustainable Development Goals [5].

Young girls face pressure to marry and have children in many societies. In many places, teenagers do not have easy access to contraceptives. Even in cases where teenagers are able to access contraceptives, they might not have the means or knowledge to procure them and use them properly. In addition, sexual abuse raises the risk of unintended pregnancy in adolescent and young girls. According to a WHO report published in 2020, 120 million girls under the age of 20 years have had some form of forced sexual contact [6]. India alone accounts for more than one-seventh of all unintended pregnancies worldwide. As per the National Family Health Survey-5 (2019-2021), women aged 15 to 19 years have 43 births per 1,000 women [5]. In 2017-19, India's maternal mortality ratio (MMR) was 103 per 100,000 live births [5]. In India, unsafe abortion continues to be the third leading cause of maternal mortality with approximately 8 women dying due to complications related to unsafe abortion every day. As per the NFHS-5 data, teenage pregnancy in India has decreased by 1% to 7.8% and female sterilization continues to be the most commonly used method of family planning in 37.9% [5]. These data indicate a need to develop preconception care guidelines suited to Indian context.

Therefore, the Indian Academy of Paediatrics called an online National Consultative Meeting on April 03, 2023, under the chairmanship of Dr MKC Nair and the National Convenor Dr Himabindu Singh. A group of experts with experience in caring for adolescents was formulated. The group planned to develop evidence-based guidelines on preconception care with the aim of improving adolescent health and ensuring a safe and healthy pregnancy with good fetal outcomes. A comprehensive search of all available research articles including randomized controlled trials, observational studies, review articles, recommendations endorsed by various authorities and other forms of studies on preconception care was made in Google Scholar, PubMed, and Cochrane database using search keywords preconception care, diabetes, metabolic syndrome, thyroid dysfunction, iodine deficiency, undernutrition, and obesity. Available guidelines from the American College of Obstetricians and Gynecologists (ACOG) [7], Position Paper on Preconception Care by the American Academy of Family Physicians (AAFP) [8], Royal Australian College of General Practitioners (RACGP) [9], Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) [10], International Federation of Gynecology and Obstetrics (FIGO) [11], Federation of Obstetrics and Gynecological Association of India (FOGSI) [12], and Guidelines from the Ministry of Health and Family Welfare (MoHFW), Government of India (GoI) were reviewed. The level of evidence (LoE) of each recommendation was graded as per the Oxford Centre for Evidence-Based Medicine (OCEBM) [13]**.** Subsequently, a physical meeting was held at Amritsar, Punjab, on October 07, 2023 during which a consensus was reached through discussions and voting and recommendations adapted to the Indian context were developed.

1. IMPORTANCE OF BEING EUMETABOLIC

Metabolic abnormalities in the mother can cause potentially adverse long-term consequences both in the mother and the baby. According to recent studies, the prevalence rates of pre-diabetes, diabetes, and metabolic syndrome among adolescents in India are 5.4%, 16.18%, and 0.56%, respectively [14]. Diabetes during pregnancy may increase the risk of miscarriage, pre-eclampsia, preterm labour, and fetal malformation, macrosomia, birth injury, and perinatal mortality. Optimal glycemic control, both before and during pregnancy, helps to reduce these

risks [15]. At the same time, maternal malnutrition can have a negative impact on obstetric and neonatal outcomes, as well as adverse long-term effects on the child's intellectual, physical, and social development [16]. Thyroid dysfunction has been associated with significant maternal and fetal complications. One important micronutrient needed for the production of thyroid hormones is iodine. Iodine deficiency disorder is estimated to affect eight million newborns and nine million pregnant women in India annually [17]. Obesity, poorly controlled diabetes, and deficiencies of micronutrients such as zinc and selenium can affect the sperm quality and fertility and consequently, the health of progeny [18].

RECOMMENDATIONS 1.0

1.a Diabetes mellitus

- Every woman who plans to become pregnant should have a diabetes screening, according to WHO criteria defined as plasma glucose ≥ 200 mg/dL for 2-hour oral glucose tolerance test (OGTT) or ≥ 126 mg/dL for fasting plasma glucose (FPG), which is measured after avoiding calories for at least 8 to 12 hours [12,19]. (LoE 1)
- Women with pre-existing diabetes mellitus should aim for a HbA1c of less than 6.5% and a fasting glucose level of 80–110 mg/dL. They should also be advised to postpone pregnancy until these objectives are met [12,19]. (LoE 1)

1.b Hypothyroidism

- Women in the preconception stage should consume 150 µg of iodine per day [12]. (LoE 3)
- Given the high prevalence of thyroid disorders in India, it is desirable to screen all women planning to conceive for thyroid dysfunction based on thyroid stimulating hormone (TSH) [12]. (LoE 3)
- Women should receive education regarding the negative effects of hypothyroidism on pregnant women such as pre-eclampsia and gestational hypertension, postpartum hemorrhage, abortion, and preterm delivery, as well as the effects on fetus and the newborn such as intellectual/neurodevelopmental impairment and learning disabilities [12]. (LoE 4)
- Women with subclinical hypothyroidism (serum TSH 2.5 to 10mIU/L and normal FT4 levels) detected during preconception should be further evaluated in consultation with an endocrinologist. Testing for anti-thyroid peroxidase antibodies is recommended to determine the need for treatment. Women with overt hypothyroidism (TSH > 2.5-3mIU/l with low FT4 levels; or TSH > 10mIU/L irrespective of FT4) should be treated [12]. (LoE 4)

1.c Hyperthyroidism

- Prior to conception, euthyroidism should be attained [12]. (LoE 4)
- If pregnancy is planned within two years, surgery is a better option than administration of radioactive iodine [12]. (LoE 3)
- Pregnancy should be delayed for at least six months if radioactive ablation therapy is used in order to restore optimal TSH levels [12,19]. (LoE 3)

2. MAINTAINING IDEAL BODY WEIGHT AND NUTRITIONAL STATUS

Both underweight (BMI of < 18.5) and overweight (BMI 25 to 29.9) and obesity (BMI ≥ 30) are associated with substantial risks for maternal and child health [9]. It is important to have a normal BMI of 18.5 to 24.9. Adequate consumption of cereals, legumes, vegetables, fruits, dairy products, and meat constitutes a balanced diet. 50% to 65% of energy should be contributed by carbohydrates, 10% by proteins, and 25% by fat. The recommended daily calorie intake for Women of Reproductive Age (WRA) is 2,100-2,400 Kcal, depending on the level of activity.

The "Choose My Plate" concept was designed by the US Food and Nutrition Department for the ease of understanding a standardised diet. The idea of "thali" was provided by the National Institute of Nutrition, Hyderabad. The dietary limitations and supplements throughout the preconceptional period are outlined in **Table I**.

Guidelines from the MOFHW and GoI

In India, pregnant women are advised to take daily oral iron and folic acid (IFA) tablets (totalling 180 tablets) with each tablet containing 60 mg of elemental iron and 500 µg of folic acid, second trimester onwards. Additionally, they are recommended to take daily calcium supplements with each tablet containing 500 mg of elemental calcium and 250 IU of vitamin D3; tablets should be taken twice daily, starting from the second trimester (14 weeks) of pregnancy and continuing for at least 180 days during gestation, as well as for the first six months after delivery while exclusively breastfeeding [20]

Healthy Lifestyles: Maintaining an ideal weight can be achieved by combining a balanced diet, frequent exercise, and enough sleep. It is advised to engage in muscle-strengthening activities two or more days a week in addition to 150 minutes of moderate physical activity per week [21]. **Table II** provides guidelines on exercise and physical fitness.

Table I Preconception Nutrition Supplementation [23,24,26]

Nutrient	*Target population*	*Recommended dose*	*Benefit*
Folic acid	All women to be continued on folic acid during pregnancy; High risk (previous NTD, anticonvulsant medication, GDM, malabsorption, BMI >30 kg/m^2)	Oral folic acid 400 µg daily for at least four weeks prior to pregnancy and for the first 12 weeks of gestation for all pregnant women; 4 mg daily for at least four weeks prior to pregnancy and for the first 12 weeks of gestation for high-risk pregnancy	Prevention of NTD such as spina bifida and anencephaly
Iodine	All women	150 µg daily while pregnant and breastfeeding	Production of maternal thyroid hormone, fetal brain and CNS development
Vitamin D	Women with vitamin D deficiency identified by blood tests	1000 IU/day (vitamin D 30-49 nmol/L)2000 IU/day (vitamin D <30 nmol/L)	Reduces risk of small-for-gestational-age babies and impaired fetal skeletal development
Iron	All pregnant women	Oral supplement with at least 60 mg of elemental iron daily (For 180 days)	Prevention of anemia
Vitamin B12	Vegans and vegetarians	250-500 µg/day oral	Prevention of neurological sequelae infants
Calcium	Women with inadequate dietary intake (<1000 mg daily)	At least 1000 mg daily Calcium carbonate	Prevention of pre-ecalmpsia

Recommendations: 2.0

1. Every woman should get her BMI determined at least once a year.
2. Women of reproductive age (WRA) with BMI ≥ 25 kg/m2 should receive specific dietary counseling, provided with strategies to enhance the quality and balance of their diets, optimise their calorie intake, and physical activity levels. They should also be encouraged to think about enrolling in structured weight-loss programmes.
3. Additionally, counseling sessions should be made available to obese men and women [12]. (LoE 3)
4. A realistic goal of 5-10% weight loss over a six-month period should be targeted [12]. (LoE 3)
5. WRA with a BMI ≤ 18.5 kg/m^2 should get counseling regarding the short- and long-term health hazards, as well as the risks associated with future pregnancies, including infertility. They should also be assessed for

Table II Preconception Exercise Guideline

Type	*Duration/Frequency*	*Intensity*	*Other information*
Aerobic	150-300 minutes of moderate intensity physical activity per week OR 75-150 minutes of vigorous activity per week OR A combination of the two	This is dependent on baseline level of fitness OR Assess via target heart rate: Age < 20 years: 140-155 beats per minute Age 20-29 years: 135-150 beats per minute Age 30-39 years:130-145 beats per minute Age > 40 years: 125-140 beats per minute	Women should aim to be active on most days of the week. Aim for exercise sessions to be no longer than 60 minutes. Ensure adequate nutrition and hydration.
Strength	Aim for two strength sessions per week on non-consecutive days	One to two sets 12-15 repetitions of each muscle group	Can use light weights, resistance bands or body weights

eating disorders and body image distortions evaluated.

6. Women who are underweight (BMI < 18 kg/m2) should be made aware of their increased risk of preterm birth, low birth weight, and birth defects like gastroschisis [12]. (LoE 3)
7. The food selections should be reviewed, and the underweight women should receive proper nutritional guidance. Treatment and screening for eating disorders, such as bulimia and anorexia nervosa, are necessary [12]. (LoE 4)

3. DECREASING SUBSTANCE ABUSE AND AVOIDING CERTAIN MEDICATIONS

In India, adult tobacco usage is prevalent in 14% of females and 42% of males [9]. Women who smoke have a higher risk of developing lung, cervical, pancreatic, bladder, and kidney malignancies in addition to cardiovascular and pulmonary disorders, regardless of whether they are pregnant. Smoking is continued in early pregnancy by nearly half of women smokers [22]. It is concerning to note that second hand smoke exposure affects more than one-third of expectant mothers and can result in low birth weight and intrauterine growth retardation [23]. **Table III** highlights the health issues related to tobacco use in WRA in the offspring [24].

Risk factors for adolescent smoking initiation include parental or familial smoking, lower socio-economic status, peer pressure, easy accessibility, media influence, academic underperformance, physical, emotional, or sexual abuse, underlying psychiatric conditions.

Evidence-based modalities for prevention, screening and treatment of substance abuse in pregnancy [10,25] include:

- Screening girls for tobacco use at all visits using the "5 As" step algorithm (Ask, Advise, Assess, Assist, Arrange)
- Various screening tools/questionnaires like SBIRT and CRAFFT questionnaire are used for assessing substance abuse in individuals.
- Using this method, couples can be advised to stop using drugs
- A family-based approach to life skill training is possible
- A behavioural approach that incorporates cognitive behavioral therapy (CBT) and rational emotive behavior therapy (REBT)
- Pharmacotherapy such as nicotine replacement therapy may be administered if necessary

Certain medicines need to be avoided in pregnancy for they may have teratogenic effects on the fetus and may also adversely affect the health of the baby as depicted in **Table IV** [26].

Recommendations 3.0

- Substance Abuse: Women who exhibit symptoms of alcoholism, tobacco dependence (smoking and smokeless tobacco), or illicit drug use should be made aware of the negative effects of substance abuse on the course of pregnancy [10,20]. (LoE 1)
- Where appropriate, pharmacotherapeutic and psychosocial interventions should be implemented to help pregnant women stop smoking [10]. (LoE 1)
- Smoking, drinking, and using drugs should be discontinued prior to conception as they can have

Table III Tobacco-use Related Health Problems

Risk Factors	*Maternal health issues*	*Neonatal health issue*
Smoking in preconception period	Infertility, delayed conception due to effect on all stages of reproductive function including folliculogenesis, steroidogenesis, embryo transfer, endometrial receptivity, endometrial angiogenesis, uterine blood flow and uterine myometrium	Damage to spermatic gene DNA may lead to cancer in offspring at later age
Smoking in Pregnancy	Spontaneous abortion, ectopic pregnancy, premature rupture or membranes, placenta previa, placental abruption	Preterm birth, low birth weight, birth defects (oral cleft, limb reduction defect, clubfoot)
Nicotine E–cigarettes in pregnancy	Addiction, Infertility, delayed conception, Hypertension, immunosuppression, altered glucose homeostasis, endothelial dysfunction	Stillbirth, preterm birth, low birth weight, small for gestational age babies
Second hand smoke exposure during pregnancy	Placental insufficiency,	Low birth weight, birth defects

Table IV Recommendation on Various Drugs During Preconception Period [20]

Drugs not to be used	*Substances not to be used*	*Drugs to be used with caution*	*Safe*
Angiotensin converting enzyme inhibitors, Atenolol, guanethidine, Oral Hypoglycemics, Valproate, Lithium, Carbamazepine, Monoamine oxidase inhibitors (MAOI) Methiazole, Radioactive iodine, Cabergoline, Indomethacin, Diclofenac, Phenylbutazone	Tobacco, Cannabis, Alcohol (any kind, any amount), Opium, Heroin, Lysergic Acid Diethylamide, Methamphetamines Codeine	Oral anticoagulants, Antibiotics, Certain oral hypoglycemics, Anti-hypertensives, Anti-epileptics Anti-tuberculous drugs, Anti-histaminics, Psychotropic drugs	Antacids, Iron, Folic acid, Calcium supplements, Insulin, Heparin, Levothyroxine

detrimental effects on the fetus and newborn. Preconceptional tobacco use by fathers has been linked to sperm DNA damage and an elevated risk of cancer in their offspring. When appropriate, medication and counseling for one or both parents should be taken into account. It is appropriate to advise pregnant women that there is no known safe level of alcohol consumption [10,27]. (LoE 1)

4. GENE-RELATED ISSUES AND GENETIC SCREENING

Regardless of a family history or any other variables, there is a background risk of approximately 5% for significant genetic abnormalities in every pregnancy. A child with an autosomal recessive or X-linked recessive disorder has a one in four chance of being born to non-consanguineous couples (1-2%), whereas consanguineous couples are at a higher risk [12]. Carrier rate of spinal muscular atrophy (SMA) is 1 in 38 individuals, while the carrier rate for thalassemia is 1 in 33 within the Indian population [28,29]

India is the world's largest country by population density and the sixth largest country in terms of land area. Due to cultural and social customs, consanguinity is common in marriages among many Indian subpopulations, which has resulted in the accumulation of genetic traits within communities [30,31]. One method of identifying couples who are more likely to have a child with a genetic disorder, particularly an autosomal recessive condition, is carrier screening or testing. The preconception phase is the best time to assess genetic risk because genetic tests can occasionally take three to six months. Preconception care should be regarded as an essential component of primary care for WRA because approximately half of pregnancies are unplanned. Carrier screening or testing can be used for identifying couples who are more likely to have a child with a genetic disorder, particularly an autosomal recessive condition The preconception phase is the best time to assess genetic risk because genetic tests can occasionally take three to six months.

Recommendations 4.0

- It is advised to have a conversation regarding the importance of carrier screening with all women and their families who are thinking about getting pregnant (preconception) and with all expectant mothers during their initial prenatal visit, irrespective of the gestational age at presentation [10,12,32]. (LoE 3)
- A thorough family history or personal indicators of bleeding disorders, muscular dystrophy, or intellectual disability should be obtained prior to conception. History of X-linked disorders like hemophilia A and B, Duchenne/Becker muscular dystrophy, and fragile X syndrome in the family need to be thoroughly evaluated in consultation with geneticist and fetal medicine expert [10,12,32]. (LoE 3)
- Provide genetic counseling to women and families who have been determined to be at risk of passing on an inherited condition due to a review of their three-generation pedigree, their ethnic background, or their previous medical and obstetrical history. As part of the informed consent procedure, direct gene mutation or expanded next generation gene sequencing testing ought to be addressed [10,12,32]. (LoE 3)
- When both partners are identified as carriers of the same autosomal recessive condition, the couple should be promptly referred for formal genetic counseling, preferably before conception or as early in the pregnancy as possible due to the complexity of the counseling/informed consent process and the 25% transmission risk to their offspring. [10,12,32]. (LoE 2)
- It is crucial to ask for history of recurrent pregnancy loss/ loss of a previous child due to unclear reasons and provide further testing and genetic counseling and

reproductive options to the couples [10,12,32,33] (LoE2)

- It is recommended that expectant couples should undergo carrier screening for the following conditions hemoglobinopathies (first detected by hemoglobin electrophoresis and complete blood count), Fragile X syndrome, cystic fibrosis and spinal muscular atrophy [10,12, 32-36]. (LoE 2)
- WRA should take folic acid 400 microgram tablet everyday before pregnancy and continue to take it till 12 weeks of gestation [36].

5. REPRODUCTIVE HEALTH IN FEMALES

Preconception healthcare is crucial for WRA to address biomedical, behavioral, and social risks to maternal health and pregnancy outcomes. Research shows it enhances birth outcomes, particularly for women with conditions like diabetes and nutritional deficiencies. However, obstacles to preconception care exist, including fragmented healthcare systems, lack of treatment for high-risk behaviors, and limited evidence-based interventions. Additionally, it's important to educate women and their partners about the declining likelihood of conception and increased risk of chromosomal abnormalities with maternal age, despite advances in assisted reproductive technology.

Obstetric history is vital for identifying modifiable risk factors linked to unfavourable outcomes in subsequent pregnancies, such as preterm birth, infant mortality, fetal loss, and neural tube defects. Close collaboration with specialists is crucial for assessing pre-existing medical conditions, with a focus on multidisciplinary care. Access to appropriate contraception is essential for stabilizing chronic conditions like epilepsy before conception.

Screening for sexually transmitted infections (STIs) and other infectious diseases: It is recommended to screen for immunity to hepatitis B, varicella zoster, mumps, rubella, and measles. STI screening is advised for both men and women, including HIV and hepatitis C with proper pre-test counseling. Patients with HIV planning pregnancy should start antiretroviral therapy to suppress viral load to undetectable levels. Pre-exposure prophylaxis for HIV-negative partners before pregnancy can reduce the risk of transmission [37,38].

Fertility issues: For women with polycystic ovarian syndrome (PCOS), oral contraceptives, hormonal patches, or vaginal hormone rings can help regulate menstruation; hirsutism or acne need to be addressed simultaneously. Regular exercise is beneficial for weight loss. Clomiphene citrate may aid in anovulatory infertility, but statins and insulin sensitizers like inositol or thiazolidinedione are not recommended [39,40].

Menstrual disorders: A sizable proportion of girls suffer from menstrual problems such as heavy, painful, and irregular menstrual bleeding. These include:

- *Primary amenorrhea*: Failure to menstruate within three years of the start of puberty-related physical changes or the absence of secondary sexual characteristics by the age of fourteen.
- *Secondary amenorrhea*: Identified two years after menarche or after missing three periods following the establishment of regular cycles.
- *Dysmenorrhea*: Painful menses not associated with pelvic pathology.
- *Dysfunctional uterine bleeding*: Prolonged, excessive menstrual bleeding that is typically caused by anovulatory cycles and lacks an identifiable organic cause.
- *Polymenorrhea*: Bleeding more frequently than every 18 days.
- *Menorrhagia*: Excessive uterine bleeding at regular intervals.
- *Metrorrhagia*: Intermenstrual bleeding.

Some of the management strategies include:

Dysmenorrhea: When cycles start to become ovulatory, primary dysmenorrhea frequently happens. Reassurance and education form the cornerstones of therapy. Secondary dysmenorrhea usually happens much later, after regular ovulatory cycles have been established. It is caused by illnesses like endometriosis, uterine or vaginal congenital anomalies, pregnancy complicationsor sexually transmitted diseases (STDs). It is treated by taking care of the underlying cause [41].

Amenorrhea: Primary amenorrhea is uncommon. Every teenager who exhibits symptoms of amenorrhea should get a pregnancy test performed. The next step is to test thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), dehydro-epiandrosterone sulfate (DHEAS) levels and karyotyping. A five-day challenge using 10 mg of medroxyprogesterone acetate per day is recommended if the hormone levels are normal. During this trial, the teen should experience withdrawal symptoms 5-7 days later. It is recommended to evaluate the patients who do not experience withdrawal bleeding or who have abnormal laboratory results by a gynecologist or endocrinologist who specializes in pediatric and adolescent gynecology.

Dysfunctional uterine bleeding: Anovulation is the most frequent reason for heavy menstrual bleeding. If the bleeding time is abnormal, she should be further assessed for von Willebrand disease. Testing for virilization and a thyroid profile may be necessary, depending on the physical examination and history. The degree of the bleeding determines the treatment:

Mild (normal hemoglobin): Menstrual calendar, reassurance, checking serum level of iron every one to two months.

Moderate (mild anemia; no hemodynamic instability): Oral contraceptives containing 50 µg of estrogenic component, such as norethindrone-mestranol or norgestrel-ethinyl estradiol, used as follows: one pill daily for four days, one pill TID for three days, one pill BID for seven days and one pill QID for fourteen to twenty-one days, after which the pills are stopped to allow for withdrawal symptoms. Thereafter, oral contraceptives are prescribed for three months in a cycle following which the serum level of iron is checked [41].

Severe menstrual bleeding (hemoglobin < 7g/dL, hemodynamically unstable): Hospitalization and administration of intravenous fluids as necessary is recommended along with monitoring for coagulopathy. Need for transfusions is determined by the clinician. Efforts should be directed at stopping the ongoing bleeding. High dose estrogen is given every four hours orally/intravenously with an antiemetic until bleeding stops, then every six hours and finally every eight hours. Iron supplementation followed by a three-month cycle of combined oral contraceptives is administered [41].

RECOMMENDATIONS 5.0

- All WRA should undergo screening for chronic medical conditions and STIs to ensure safe pregnancies and optimal outcomes. (LoE 2)
- Appropriate management of PCOS, menstrual disorders and nutritional deficiencies is important in women of reproductive age groups. (LoE 2)

6. REPRODUCTIVE HEALTH IN MALES

Reproduction in men has an impact on fertility and sexuality. Important part of male reproductive system consists of the prostate gland, penis, testicles, epididymis, and vas deferens. These body parts are involved in ejaculation and the production of semen [42]. Typical issues associated with male reproductive health consist of:

Male contraception: Use of condoms made of latex or polyurethane offers additional benefits of reducing the chance of STIs; STIs are not prevented by lambskin condoms. Vasectomy is a surgical procedure which may take up to three months to take complete effect; till then a backup method of contraception is recommended. Similar to other sterilization techniques, vasectomy is regarded as a long-term method of contraception [43].

Sexually transmitted infections (STIs): To prevent STIs, it is advisable to ascertain the risk of acquiring an STI by having a discussion with the healthcare provider. The partner's past sexual history and health issues need to be considered and relevant tests should be advised to confirm any suspicion. Vaccinations against hepatitis A, hepatitis B, and human papilloma virus help prevent STIs. Counselling regarding safe sexual behavior such as proper and consistent use of latex condoms are recommended.

Male infertility: Infertility is defined as the inability of a man or woman to conceive after a year of sexual activity without the use of birth control. In general, problems with male partner, female partner, or unknown factors account for one-third of cases of infertility, while problems with both partners account for another third. The inability of the testicles to produce sperm or a complete lack of sperm which affects 10% to 15% of cases, hormone imbalances and obstruction of sperm motility are among the important causes. Varicocele is one of the most frequent causes of this condition [44]. To ascertain the cause of infertility, past medical history including history of any injuries to penis or testicles, any recent high fevers, and any childhood illnesses like the mumps should all be covered. Physical examination to detect infection, hernia, varicocele, or any indicator of underlying hormonal imbalance deficiency such as reduced muscle mass, decreased facial and body hair and increased body fat are mandated [45]. Investigations include:

- Semen analysis with at least two separate semen samples collected least one week apart and with at least 3 days of abstinence preceding the first specimen is recommended.
- Hormonal testing including serum follicle-stimulating hormone (FSH), testosterone, luteinizing hormone (LH), prolactin, thyroid-stimulating hormone (THS, optional), and estradiol (optional) assay is indicated if there is a low sperm count and concentration or clinical findings are suggestive of an endocrine disorder or impaired sexual function.
- Testicular biopsy may be indicated in some cases to exclude spermatogenic failure. Testicular biopsy is typically done in men suspected of ductal obstruction who would present with azoospermia, normal hormonal screening tests and normal-sized testes.
- Karyotype is recommended if there is low testosterone

with high FSH and LH (primary hypergonadotropic hypogonadism). This in turn would affect both sperm production (FSH) and testosterone levels (LH).

- Genetic screening and chromosomal testing may be indicated with azoospermia or severe oligozoospermia as chromosomal defects are more common in infertile men. The common genetic factors which are associated with infertility in males are impaired testicular function due to chromosomal abnormalities (Klinefelter syndrome and XX DSD), isolated spermatogenic impairment due to Y chromosome microdeletions, and congenital absence of the vas deferens due to cystic fibrosis transmembrane conductance regulator (CTFR) gene mutation [46-49].

Treatment

Treatment should be directed at the underlying cause. Evidence-based treatment for improved fertility may be suggested if no problems are found. Surgery is one form of treatment for anatomic abnormalities or damage to the reproductive organs. Medications for treating conditions like erectile dysfunction and hormone imbalances that affect male fertility may be needed. Blockages in the tubes that carry sperm and varicocele can be fixed surgically [50-53].

Recommendations 6.0

- Aromatase inhibitors (AIs), human chorionic gonadotropin (hCG), selective estrogen receptor modulators (SERMs), or a combination thereof is recommended for infertile men with low serum testosterone. (LoE 3)
- Supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose. (LoE 3)
- For men with idiopathic infertility, a clinician may consider treatment using an FSH analogue with the aim of improving sperm concentration, pregnancy rate, and live birth rate. (LoE 2)
- Surgical varicocoelectomy should be considered in males attempting to conceive, who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men [54]. (LoE 2)

7. IMMUNIZATION

Preconception vaccinations lower the risk of in-utero disease transmission, reduce maternal morbidity and mortality and passively transfer antibodies to the fetus and newborn. These include:

1. Influenza vaccine: Women who receive the vaccine have a much lower incidence of low birth weight and premature deliveries [55]. Babies born to mothers who had received influenza vaccine had a lower incidence of influenza infections during infancy [56]. Many nations now advise all pregnant women to get vaccinated against influenza in light of these findings [57].

2. Human Papilloma Virus (HPV) vaccine: Children of vaccinated mothers are protected against laryngeal papillomatosis as well as genital warts, cervical, rectal, anal, vulval, and vaginal cancers. There are currently two vaccines that can be used in individuals between the ages of 9 and 26 years: the quadrivalent and the nonavalent [58].

3. Conjugate Pneumococcal vaccine (13 valent) protects against invasive pneumococcal disease in people with HIV, diabetes, functional or anatomic asplenia, and chronic lung and heart disease. A single dose is given intramuscular. One year after the PCV 13 dose, the polysaccharide pneumococcal vaccine 23 (PPSV 23) is given to provide additional serotype coverage.

4. Japanese Encephalitis vaccine if administered before becoming pregnant, it protects against significant mortality and morbidity in endemic areas. Before visiting an endemic area, it can be obtained as a two-dose schedule given one month apart [59].

Vaccines that prevent fetal disease [60] include:

1. Measles, Mumps, and Rubella (MMR) vaccine: Measles infection during pregnancy has been linked to low birth weight, premature birth, and spontaneous abortions. Mumps causes first trimester abortions. A first-trimester rubella infection causes congenital rubella syndrome, a fatal condition with significant morbidities in the unborn child. Congenital rubella syndrome has become much less common as a result of vaccination campaigns for girls. If a woman has not received the MMR vaccine, she can receive two doses, spaced at least four weeks apart, with the recommendation that she should not to become pregnant for at least 28 days after the vaccination.

2. Hepatitis B vaccine: If a woman is not vaccinated for hepatitis B for any reason, she should be tested for hepatitis B and if the results are negative, the three-dose schedule is administered before she becomes pregnant. If a mother is found to be HBsAg-positive, she should be followed-up closely to ensure that the infant receives hepatitis B Immunoglobulin and the zero dose of hepatitis B vaccine within 12 hours after birth. The infant must be followed up closely to ensure that the infant completes the recommended Hepatitis B vaccine schedule.

3. Tetanus, Diphtheria, acellular Pertussis (TdaP) vaccine: Immunizing a fetus or newborn before or during

pregnancy with a vaccine containing tetanus, pertussis, and diphtheria confers passive immunity. As of now, all expectant mothers should receive a single dose of the TdaP/dT vaccine between weeks 27 and 36 of gestation, earlier being preferable and should do so each time they become pregnant.

4. Varicella vaccine: An infection with varicella during the first or early second trimester causes limb atrophy, skin scarring on the extremities, abnormalities in the central nervous systemand issues with the eyes. All WRA who have never had varicella are eligible for a 2-dose regimen, which offers 98% efficacy when administered 4 to 12 weeks apart. Due to the live vaccine's contraindications, pregnancy should be avoided for up to one month following vaccination.

Recommendations 7.0

All pregnant women should receive the following vaccines [57-60]:

During pregnancy:

a) *TdaP*: One dose TdaP given between 27 to 36 weeks of gestation

b) *Influenza vaccine*: One dose inactivated influenza vaccine given after 26 weeks of gestation (may be given earlier in the event of a pandemic). Live intranasal influenza vaccine cannot be given to pregnant women.

Before pregnancy:

a) *Hepatitis B*: 3-dose schedule at 0, 2, 6 months (if not taken earlier)

b) *Varicella*: Two doses spaced 4 to 12 weeks apart (if no prior varicella infection and no history of the illness)

c) *MMR*: If not taken earlier, two doses spaced four weeks apart

d) *HPV*: Two doses (0, 6 months) of the quadrivalent or nonavalent HPV vaccine for children aged 9 to 15 years; three doses (0, 2, 6 months) for adults aged 15 to 26 years. HPV vaccination is licensed for upto 45 years of age.

e) *Conjugate pneumococcal vaccine* (PCV-13) in special situations

f) *Japanese encephalitis vaccines*: Two doses given in an endemic zone separated by a month.

8. BODY IMAGE, COSMETIC CONCERNS AND DENTAL HYGIENE

Pregnancy, a profound event lasting approximately 40 weeks, brings about significant biopsychosocial changes. According to the Developmental Origins of Health and Disease (DOHaD) theory, environmental factors in critical windows of development, shape health and developmental outcomes, possibly via epigenetic mechanisms [61]. Preconception women fall into two groups

1. Those intending pregnancy, open to lifestyle modifications.
2. Unplanned pregnancies, including those from casual sex or out of wedlock, pose a high-risk group less receptive to disfiguration concerns, risk factors, and guidelines.

8.1 Body image

Pre-conception fear of body changes leading to obesity may result in dissatisfaction, eating disorders, and anxiety/depression, affecting post-natal care. Up to 45% of pregnant women experience dissatisfaction. Unhealthy epigenetic-environmental factors can harm the fetus.

Concerns for pre-conception women: [62]

a) Pregnancy-related body changes and image issues

b) Dietary deficiencies from restricting food to minimize weight gain

c) Prospective postnatal body image/breastfeeding

d) Functionality issues

Recommendations 8.1

1. Provide preconception counseling to avoid metabolic syndrome.
2. Address substance abuse as a stress-coping mechanism.
3. Limit excessive use of social media [62,63]. (LoE 2)

8.2 Cosmetics

Cosmetics pose risks during early pregnancy (5-8 weeks), with 5-20% of pregnancies exposed to retinoids showing fetal retinoid syndrome. Several cosmetics contain harmful chemicals like butylated hydroxyanisole and coal-tar dyes which can induce epigenetic modulation, endocrinal disruption, DNA repair failure, oxidative stress, and ovarian toxicity.

Recommendations 8.2

1. Reduced use of cosmetics during the perinatal period.
2. Use simple, rinsable products with known ingredients and no perfume.
3. The use of essential oils, perfumes, nail polish remover, and hair colors should be avoided by nursing moms.

4. After using volatile cosmetics, particularly sprays and aerosols, let the room air out [64]. (LoE 2)

8.3 Dental Hygiene

During pregnancy, numerous physiological, hormonal, and psychological changes happen in the woman's body; it may lead to fluctuation in oral hygiene practices, eating patterns, and multiple oral health problems in 60-75% of pregnant women. It may be associated with obstetric complications like eclampsia pregnancy, small-for-date babies, and premature birth.

Maternal diet and precautions may be helpful to the fetal oro-dental growth, which starts from 12 weeks of fetal life.

Recommendations 8.3

1. Avoid frequent intake of sugary snacks.
2. Brush regularly (morning and night).
3. Preconception dental check-up is mandated.
4. Undertake routine dental care procedures under local anesthesia
5. The dentist's prescription must be reviewed by obstetricians. Dentists also be provided with medical history.
6. Consider dental *X*-rays with proper shielding [65]. (LoE 2)

9. MANAGING RELATIONSHIPS - PREMARITAL AND CONJUGAL

Premarital relationship is a period in which two distinct people who do not know each other learn to know and understand each other as well as form bonds that are required to live together before they decide to marry [66]. Conjugal relationship is related to marriage or married persons and their relationships. The changing lifestyle of adolescents, delay in marriage, premarital relationships, premarital sex, live-in relationships, increasing adolescent pregnancy and STIs, increasing prevalence of separation and divorce are proven by various studies [67-69]. Sensitization of adolescents and couples to right knowledge and skills to balance relationships is much needed. Studies indicate rates of premarital sex range from 17% among school children to 22% among young workers in north India [70]. Multinomial analysis clearly shows the reasons underlying delayed marriage being education, ambitions, wealth quintile, and mass media [67]. The 2011 Census of India shows that the average age at which women marry in India has risen to 21years [71]. Divorce rate in India is on the rise due to various reasons like lack of communication, infidelity, lack of intimacy and interference by family or friends.

Premarital education and counseling on relationship balance and management

Clinical and Educational Frameworks Schumm and Denton identified four major approaches to pre-marriage preparation [71]. Enrichment, or process-oriented couple learning facilitation; instructional counseling, which entails more didactic, problem-focused training on marital matters; generalized education akin to that of marriage courses in high school and college; and therapeutic examination of general or specific relationship issues. Couples' strengths are developed, competency is emphasized, and preventive education is given through active skill development in enrichment programs. Community-based programs like the Couple Communication Program (CCP), Parent Assessment Program (PAP), Relationship Enhancement (RE), and Premarital Relationship Enhancement and Prevention (PREP) aim to build communication, problem-solving, and support skills [71].

Recommendations 9.0

- Raise community awareness on the advantages and disadvantages of (pre)marital relationships (e.g., problem-solving abilities, cohabitation, violent past).
- Instil practical and interpersonal skills in adolescents and young adults.
- Extend distribution methods to include internet resources for couples and providers, self-directed materials, and community seminars.
- Make extra efforts to connect with couples and people who are more vulnerable.
- Include (pre)marital counseling in currently running government initiatives, such as RCH-A (ARSH) for teenagers [67-71]. (LoE 3)

10. MENTAL WELL BEING AND SUPPORT SYSTEM

Mental well-being, a pivotal preconception health indicator, should be integrated into public health interventions. This includes addressing risk factors on three levels: biological (days to weeks prior to the development of the embryo), individual (willing decision to become pregnant), and public health (months or years prior)

The National Institute for Health and Care Excellence recommends discussing pregnancy planning with all WRA with any mental health history. One in four WRA face mental disorders with rising prevalence in young pregnant women [72]. Depression and anxiety dominate preconception mental disorders, often accompanied by substance abuse [73].

Inadequate preconception mental health increases the chance of unfavorable results in offspring as well as pregnancy. Postpartum psychosis is more common among women with a history of anxiety disorders, panic disorder, obsessive-compulsive disorder (OCD), and pre/postpartum depression who have mental illnesses, such as bipolar disorder, either current or former. Antipsychotics and mood stabilizers are frequently prescribed medications, as they are frequently needed. Because the data on fetal and neonatal outcomes are inconsistent, antidepressants are used with caution (1-5% of pregnant depressive women) [74]. The most often used atypical antipsychotic medication during pregnancy is quetiapine. Aripiprazole, olanzapine, and ziprasidone are commonly used with no significant association with congenital malformations.

Pregnancy-related anxiety is common and influenced by factors like a history of mood disorders, body changes, financial concerns, and new responsibilities. Hormonal shifts during pregnancy (e.g. significant changes in estrogen and progesterone hormone levels can affect levels of neurotransmitters), previous miscarriages, sleep issues, concerns about relationships, the baby's health, and the delivery experience contribute to maternal anxiety. While some anxiety is normal and protective, excessive anxiety may impact fetal and neonatal outcomes.

Prenatal depression is more common among women who are carrying a child with health problems or special needs, dealing with stressful life events (divorce, health issues, financial problems, work troubles), expecting twins or triplets, unplanned pregnancy, lack of supportive partner or network of friends and family during pregnancy, and those who face difficulties in conceiving due to infertility

Pregnant women facing domestic violence endure significant psychological distress, emphasizing the urgent need for screening and support in antenatal services. Physical and psychological abuse, rooted in illiteracy, poverty, and community indifference, is prevalent. Victims receive less antenatal care, leading to a 2.59 - 2.37 times higher risk of perinatal and neonatal mortality respectively [75]. Remarkably, 3.8% of battered women require medical attention and 4.5% require hospitalization [75]. In order to address this and lower domestic violence among Indian women, women's education, economic independence, and empowerment must be prioritized.

Recommendations 10.0

1. Lifestyle changes like regular physical activity and nutritious diet during pregnancy will aid reduction in stress, anxiety, and other mental health issues [76]. (LoE 2)
2. 7-8 hours of uninterrupted sleep is recommended. Insomnia should be identified early and treated according to the causative factor [77]. (LoE 1)
3. *Psychoeducation*: Women should be given information on the effects that pregnancy and childbirth can have on mental wellbeing and the signs of perinatal mental health problems to look out for. Conversations should be open, encouraging dialogue and active listening, and confidential [78]. (LoE 3)
4. Mindfulness practices may be beneficial for outcomes in conditions like anxiety, depression [79]. (LoE 1)
5. Medication considerations: For severe cases requiring medications, counselling on various treatments available should be given to choose medications which may cause minimal harm to the fetus [80,81]. (LoE 3)
6. Therapeutic approaches: Consider CBT (Cognitive Behavioural Therapy) for challenging maladaptive thoughts with a focus on anxiety management strategies adapted to pregnancy [82]. (LoE 1)
7. Alternative interventions: Yoga has been proven to be very effective in reducing depression and anxiety during pregnancy. Other interventions are massage therapy, meditation and acupuncture [83]. (LoE 1)

CONCLUSION

Although there have been major advances in the field of medicine and perinatal care, birth outcomes are worse in both the developing and developed countries alike. Many babies are born early or have low birth weight leading to other complications. Hence, the concept of preconception care takes precedence when it comes to health of children, the guidelines listed above for men and women are not just for planning a pregnancy but for taking control of their lives and choosing healthy habits.

To be able to reduce maternal and childhood mortality and morbidity, we need to address any mental health issues related to pregnancy, childbirth, infancy, childhood, adolescence and adulthood. This will include health education and promotion, risk assessment, specific counseling, intervention before pregnancy. These guidelines when properly implemented in the community will bring about a positive change in the health and wellbeing of adolescents, adult men and women and thereby improve subsequent pregnancy and child health outcomes.

These guidelines are provided in ten different domains – being eumetabolic, nutrition and healthy lifestyle, avoiding substance abuse, genetic screening, reproductive health, immunization, body image/cosmetics/dental

Box 1 Preconception Care Checklist

Diet

- Nutritional requirements including folic acid supplementation
- Advice on a healthy diet with special emphasis on micronutrients

Weight

- Appropriate advice for underweight and overweight WRA

Exercise

- Advise 150 minutes of exercise per week or 30 minutes on most days

Genetic screening

- If indicated from personal/family history or ethnic background

Smoking/alcohol/illicit drugs

- Assess intake and provide appropriate advice (See **Tables III** and **IV**)

Psychosocial aspects

- Screen for domestic violence
- Screen for pre-existing mental health conditions and provide appropriate management

Medical conditions

- Review current disease status (Diabetes mellitus and thyroid dysfunction) and treat accordingly in collaboration with specialists, if required

Environment

- Assess work, home and recreational environments

Dental health check

Screening for sexually transmissible infections and other infectious diseases

- Measles, mumps, rubella, varicella zoster, hepatitis B
- Human immunodeficiency virus and hepatitis C with appropriate pre-test counseling
- Screening for cervical cancer
- Appropriate advice on vaccination.

health, handling relationships, mental well-being/support system. It can be used as a ready reckoner in the community for bringing about a positive change. See **Box 1.**

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INVITED COMMENTARY

Autism Screening in India: Many a Chasm to Bridge

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Autism is a relatively new entrant into the arena of neurodevelopmental disorders. Though the earliest formal diagnosis was suggested by the Swiss psychiatrist Paul Eugen Bleulerback in 1911, it was only later in the 40s that the American psychiatrist Leo Kanner (1943) and the German pediatrician Hans Asperger (1944) presented their findings, to set the ball rolling. Interestingly, literature from India appeared in the same year by an Austrian Pediatrician, A Ranold working in Darjeeling [1]. Since then, both the disorder and the relevant research has been progressing at a prolific rate.

Today, Autism Spectrum Disorder (ASD) is a major neurobehavioral problem of global concern. As of 2020 CDC reports, 1 in 36 children in USA come under the spectrum [2] and autism occurs across all racial, ethnic and socioeconomic groups. The estimated prevalence in India is 1.12 (0.74-1.68) per 100 children aged 2-9 years [3], i.e., 1 in every 68 children is affected with autism. With our huge child population, the total numbers contribute to a major portion of the global prevalence. Hence, we bear a grave responsibility to detect and treat these children across the country.

Early signs of autism are often picked up by parents between 6-18 months of age and typical symptoms are evident by 2-3 years. Early detection and early intervention has definite positive developmental and behavioral outcome. Studies have shown that early interventions not only limit deterioration, but may also lead to such functional improvement that some children evolve out of the autistic traits [4]. Unfortunately, we encounter a detection gap, wherein either the diagnosis occurs late or is missed totally, leading to a tragic loss of the golden opportunity. The reasons are multiple, including dearth of trained professionals and para-professionals, non-availability of screening tools and programs, parental denial and lack of awareness.

Ideally, all children should be screened by 3 years of age. The American Academy of Pediatrics (AAP) recommends screening for ASD at both 18- and 24-month well visits [4]. Indian Academy of Pediatrics (IAP) advocates universal ASD screening at 18 and 24/30 months for which M-CHAT-R/F, Trivandrum Autism Behavioral Checklist (TABC), and Social Communication Questionnaire (SCQ) are recommended [5].

Numerous screening tools are in use today, both internationally and nationally [6]. Some of the well-known international tools include:

- Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT R/F) : for 18-30 months; 20 item questionnaire
- Developmental Behavior Checklist: Early Screen (DBC-ES): for 18-48 months; Developmental Behavior Checklist: Autism Screening Algorithm (DBC-ASA): 4-18 years; Autism Behavior Checklist for 3-14 years
- Pictorial Autism Assessment Schedule (PAAS)
- Three Item Direct Observation Screen (TIDOS)
- Social Communication Questionnaire (SCQ) (Lifetime and Current versions): 40-item questions, in a parent-report format, based on the Autism Diagnostic Interview (ADIR) validated for 4+ years. SCQ Lifetime can be used below 4 years. This has not been translated, adapted or validated for Indian settings.

Of these, only the M-CHAT R/F is in use in India. It has been translated into multiple Indian languages, Although, none have of these versions have been adapted to Indian cultural norms or validated till date. The present research published in this issue of Indian Pediatrics [7] is a commendable step forward in this regard. There are quite a few Indian tools in vogue, which meet our needs but may not be standardized for global research. The ones best known include:

- The Indian Autism Screening Questionnaire (IASQ), derived from the Indian Scale for Assessment of

Autism (ISAA) is a 10-item questionnaire with yes/no answers which is meant for children aged 3-18 years [8]

- INCLEN Diagnostic Tool for ASD (INDT-ASD)
- Trivandrum Autism Behavior Checklist (TABC), a tool in Malayalam and English, developed and validated at Child Development Centre (CDC), Kerala, and has a 80% sensitivity and 91.1% specificity for children aged 2-6 years.
- RBSK–Autism Specific Questionnaire (RBSK-ASQ) has 3 'yes/no' questions for each age-group of 15-18 months and 18-24 months [10].

All of these are designed for use in the general population by minimally trained workers. The TABC has been tried out in the Integrated Child Development Services (ICDS) Scheme centres by Anganwadi workers successfully. To ensure screening of all children across the country through front-line workers, a simple, easy to administer, validated tool of high sensitivity, specificity and convergent validity, written in a local language and customized to our social and cultural norms is essential. For a pan-India reach out autism screening needs to be incorporated in the ground level health assessment of small children by field level workers (ASHA and Anganwadi workers), who, in turn, need to be trained appropriately to use the tools. Various isolated projects have shown promising results with screening programs conducted by para-professionals. Another approach is screening at the pediatrician's clinic, which has been initiated by IAP through its flagship program on Early Childhood Development training of all its members, which also includes autism screening with M-CHAT at 18 and 24 months.

For a parity in screening across the country, a set of validated tools may be considered. M-CHAT is useful till 30 months of age, for older children TABC or Indian Autism Screening Questionnaire (ISAQ) may be useful. Such a program, with proper documentation, can produce an extremely valuable dataset for the world to utilize. India with its huge number of children with neurobehavioral disorders growing up in diverse situations of culture, customs and socio-economic conditions poses as a unique repository of resources for us to explore, for the benefit of children across the globe. If we can build a solid mechanism for public awareness and early identification of autism and document the same, we can be instrumental in catalyzing a global movement in the field.

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ORIGINAL ARTICLE

Validation of the Hindi Versions of Three Autism Specific Screening Tools (M-CHAT-R/F, RBSK-ASQ and TABC) Widely Used in India in 16-30-Month-Old Children

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ABSTRACT

Objective: To determine the diagnostic accuracy of MCHAT-R/F, RBSK-ASQ and TABC for screening children aged 16 to 30 months for autism spectrum disorder (ASD).

Method: Children aged 16 to 30 months were recruited from the pediatrics department. Those with known neurodevelopmental disorders, disabilities, severe medical illnesses, unavailable mothers, or lack of maternal understanding of Hindi, were excluded. The three index tools were translated into Hindi; each tool was piloted on 25 mothers and modified accordingly. The researcher was trained in administration, scoring and interpretation of the three tools. After enrollment the index tools and Developmental Profile (DP-3) were administered to each participant. The reference tool was a comprehensive assessment by experts that included clinical evaluation, computation of DP-3 scores, and application of diagnostic criteria of ASD; the final diagnosis being ASD or Non-ASD.

Results: Sensitivity and specificity of M-CHAT-R/F were 95.2% and 94.4%, of RBSK-ASQ were 100% and 93.9%, and of TABC were 100% and 94.4%, respectively. Convergent validity was high (Spearman's correlation coefficient 0.98). Test-retest and inter-rater reliability of each tool was excellent (Intra-class correlation coefficient 1.00).

Conclusion: All three tools had acceptable psychometric properties, high convergent validity and excellent test-retest and inter-rater reliability.

Keywords: *Developmental screening, Diagnostic accuracy, LMIC, Psychometric properties, Reliability*

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INTRODUCTION

Autism spectrum disorder (ASD) is a common neuro-developmental disorder of childhood characterized by difficulties in social communication and social interaction, and the presence of restricted and repetitive patterns of behaviors, interests, and activities [1]. A community-based study from India reported a prevalence of 0.8-1.3% in children aged 2-9 years [2]. Manifestations may be so subtle in the early years that they fail to elicit serious concerns in caregivers and are disregarded as 'shyness' typically associated with young children. Early detection is low unless actively sought by using ASD-specific screening tools. Screen positive children identified as 'at high risk for ASD' warrant further in-depth evaluation. If ASD gets diagnosed subsequently, timely holistic intervention translates into better outcomes. Thus, ASD is a public health problem that requires 'universal' screening i.e., it should be done for all children, even if they appear to be developing typically.

Screening for a specific disorder like ASD requires the administration of a narrow band screening tool with 'acceptable' psychometric properties. This has been defined as a combined sensitivity and specificity of >70% in the intended population [3]. Lower sensitivity means children with ASD will be missed; whereas lower specificity would result in misdiagnoses with unwarranted parental stress and expenditure. A systemic review on suitable screening tools for developmental delay and ASD for low- and middle-income countries (LMIC) identified certain optimal features for ASD specific tools [4] which include under 30 minutes needed to administer, easily accessible, free or inexpensive, suitable for use by community health workers (CHW) or para-professionals without requiring extensive training, and successful use in at least one LMIC. Only three of the 34 tools in use globally that were reviewed, satisfied these criteria [4], *viz.*, Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F) [5]; Pictorial Autism Assessment Schedule (PAAS), and Three Item Direct Observation Screen (TIDOS).

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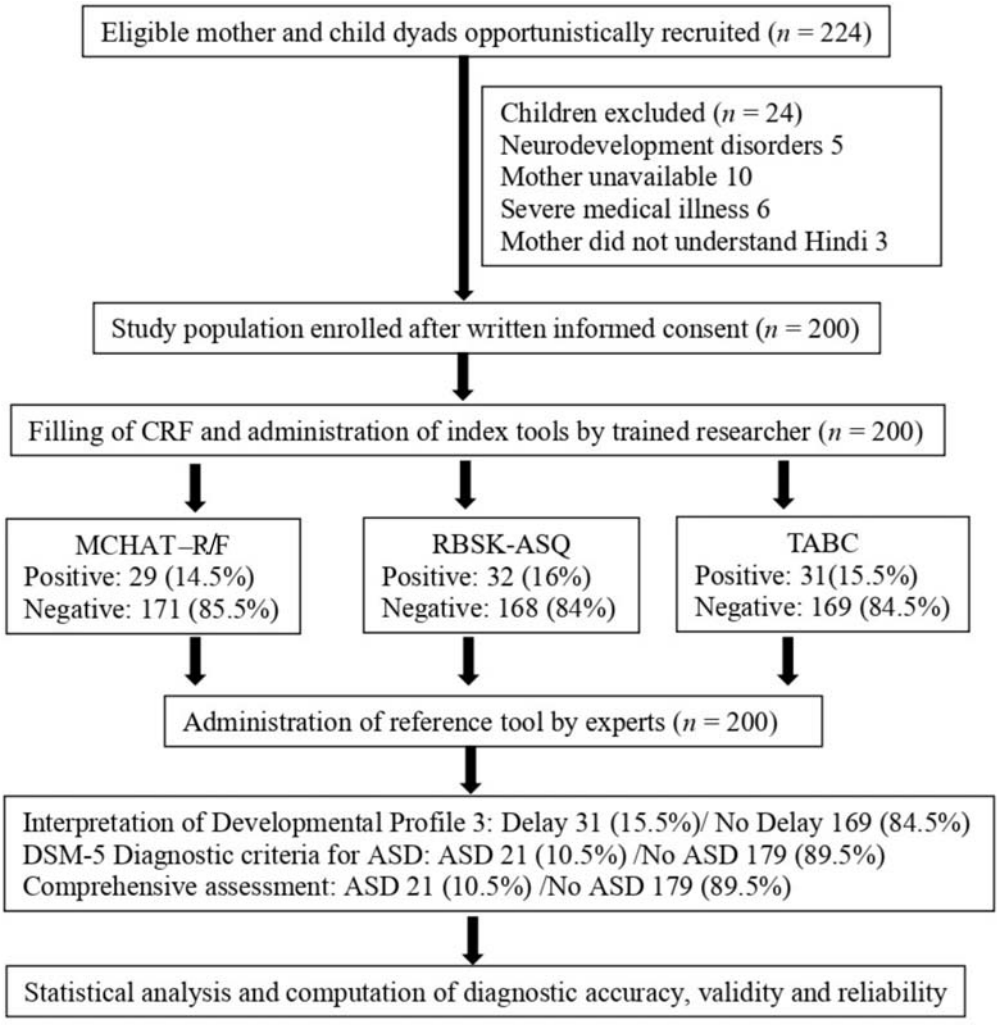
The 2016 UNICEF model on developmental screening states that a country should use tools appropriate for their needs and population [6]. Indian Academy of Pediatrics (IAP) advises universal screening for ASD at 18 and 24/30 months along with developmental screening [7,8], and recommends M-CHAT-R/F [5], Trivandrum Autism Behavioural Checklist (TABC) [9], and Social Communication Questionnaire (SCQ). Rashtriya Bal Swasthya Karyakram (RBSK), an initiative of the Government of India to screen for diseases, deficiencies, defects at birth and developmental disabilities in children uses RBSK–Autism Specific Questionnaire (RBSK-ASQ) to screen for Autism across India [10]. PAAS and TIDOS are generally not used in India.

MCHAT-R/F is used for toddlers between 16 and 30 months of age. It can be administered by parents (with education level > 6th standard) or service providers. Though translated into several Indian languages, these versions are neither culturally adapted, nor validated [11]. The tool is primarily used by pediatricians and has gained popularity after IAP NURTURE started training pediatricians to administer it at the age-appropriate well child visits [12]. TABC is an indigenous tool available in Malayalam and English and used by CHW in Kerala for children aged 2 to 6 years [9]. The RBSK-ASQ has two versions for use in children aged 15-18 and 18-24 months. The English format is available in the public domain [10], but translations are being used locally. SCQ has not been



ASD Autism spectrum disorder, CRF case recording form, DSM-5 Diagnostic and Statistical Manual of Mental Disorders, 5th edition, MCHAT-R/F Modified Checklist for Autism in Toddlers, Revised/ Follow-up, RBSK-ASQ Rashtriya Bal Swasthya Karyakram - Autism Specific Questionnaire, TABC Trivandrum Autism Behavioural Checklist

Fig. 1 Flow of participants from recruitment, through enrollment, administration of index tools and reference tool to statistical analysis

translated, adapted or validated for Indian settings. Additional drawbacks are expense, copyright issues, and restricted use by professionals who do not usually come in contact with typically developing children.

A critical research lacuna identified on applying the LMIC parameters to three commonly used tools (**Table I**) was the lack of robust scientific literature pertaining to validation. Thus, we aimed to determine the diagnostic accuracy of Hindi versions of M-CHAT-R/F, TABC, and RBSK-ASQ for screening children aged 16 to 30 months for ASD.

METHODS

A hospital-based study of diagnostic accuracy was conducted over 18 months (January 2021 to June 2022) after obtaining approval from the Institutional Ethics Committee. In the preliminary phase we translated the index tools (M-CHAT-R/F, TABC and RBSK-ASQ) into Hindi after obtaining permission from the competent authorities for each tool. The standard WHO protocol was used involving adaptation, translation and back-translation by language and subject experts [13]. The following modifications were made by group consensus ensuring maintenance of context (i.e. no change in face validity): the language of M-CHAT-R/F was made simpler than the Hindi version available on the website, and culturally acceptable examples were included (i.e., vacuum cleaner replaced by whistle of a pressure cooker). We used the provider completed format rather than the parent completed one, as developmental awareness of caregivers from LMIC is not considered optimal, irrespective of educational level [4]. No changes were required in RBSK-ASQ or TABC. The tools were piloted on 25 mothers to identify the possible difficulties in maternal understanding and/or issues in administration of the tools by the researcher. No issues were identified with M-CHAT-R/F or RBSK-ASQ, but it was observed that understanding and ease of administration improved on converting the phrases of TABC into questions. TABC was administered to a different set of 25 mothers within a week in the revised format, and no difficulties were detected.

The researcher was trained to administer, score and interpret each index tool as per the operational guidelines, until deemed competent by the experts. In M-CHAT-R/F (comprising of 20 questions) atypical behaviors are scored '1'and typical behaviors '0'. A child is considered 'at low risk', 'at medium risk' and 'at high risk' if the total score is 0-2, 3-7, and 8-20, respectively [11]. In the 20-item TABC, symptoms are organized into four domains: social interaction, communication, behavioral characteristics, and sensory integration. Scoring is based on frequency by a Likert scale: never 1, sometimes 2, often 3, and, always 4. A child is considered 'non-autistic' if the total score is 20-35; 'mild autistic' if 36-43, and 'severe autistic' if ≥ 44 [9]. Both the RBSK-ASQ versions have three questions with dichotomous answers (Yes/No). For the purpose of the study, a child was considered screen positive for ASD based on satisfaction of the standard operating procedure for each tool: M-CHAT R/F -'at high risk', or persistence of 'at medium risk' on re-evaluation after a month; TABC - total score > 35, and; RBSK-ASQ - if the response was 'no' for items 1 and 2, and 'yes' for item 3 (15-18 months format); and 'no' for items 1 and 3, and 'yes' for item 2 (18-24 months format) [10].

The reference tool was a comprehensive assessment for ASD based on history, clinical evaluation and

Table I Psychometric Properties of Modified Checklist for Autism in Toddlers, Revised with Follow-up, Rastriya Bal Swasthya Karyakram –Autism Specific Questionnaire, and Trivandrum Autism Behavioral Checklist

Psychometric properties	*M-CHAT-R/F*	*RBSK-ASQ*	*TABC*
Sensitivity (%) (95% CI)	95.2 (77.3, 99.2)	100 (84.5, 100)	100 (84.5, 100)
Specificity (%) (95% CI)	94.4 (90.0, 96.9)	93.9 (89.3, 96.5)	94.4 (90.0, 96.9)
Positive Predictive Value (%) (95% CI)	66.7 (48.9, 80.8)	65.6 (48.3, 79.6)	67.4 (50.1, 81.4)
Negative Predictive Value (%) (95% CI)	99.4 (90.4, 96.9)	100 (97.8, 100)	100 (97.8, 100)
Positive Likelihood Ratio (95% CI)	17.1 (13.9, 20.8)	16.3 (13.6, 19.5)	17.9 (14.7, 21.8)
Negative Likelihood Ratio (95% CI)	0.05 (0.01, 0.4)	0	0
Convergent Validity (SCC)	0.9	1.00	1.00
Test-retest Reliability (ICC)	0.9	1.00	1.00
Inter-rater Reliability (ICC)	0.9	1.00	1.00

CI Confidence interval, ICC Intra-class correlation coefficient, M-CHAT-R/F Modified Checklist for Autism in Toddlers, Revised with Follow-up, RBSK-ASQ Rashtriya Bal Swasthya Karyakram-Autism Specific Questionnaire, SCC Spearman Correlation Coefficient, TABC Trivandrum Autism Behavioural Checklist

Note: Cronbach's alpha was the reliability coefficient used to express ICC and SCC

observation, assessment of developmental status by 'Developmental Profile, 3rd edition' (DP-3) [14] and, application of Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria for ASD. These criteria are considered fulfilled when all three deficits in social communication (A); at least 2 of 4 criteria of repetitive behaviors, activities or interests (B); and criteria C (since early developmental period), D (causing significant functional impairment), and E (not better explained by other conditions) are present [1]. DP-3 assesses acquisition of skills in five developmental domains (physical, socio-emotional, communication, cognition, and adaptive behavior) on the basis of which domain-wise standard scores (SS) and an overall General Developmental Score (GDS) are computed; in either < 70 is considered as 'delay'. The study definition of ASD was a clinical diagnosis ascertained by expert evaluation based on the comprehensive assessment. In children < 24 months if the DSM-5 criteria were not satisfied, delay or dissociation in social-emotional and communication domains compared to the other domains was considered diagnostic.

The study population included children aged 16 to 30 months who were opportunistically recruited from the pediatric outpatient (i.e. those presenting with minor illnesses or coming for immunization) and inpatient departments (at discharge). Children with known neuro-developmental disorder/ disability, any severe medical illness, absence of mothers, or lack of maternal understanding of Hindi were excluded. We calculated a sample size of 200, assuming 10% prevalence of children 'at risk of ASD', sensitivity and specificity of M-CHAT-R/F of 50% [15] and 80% [16] respectively (as reported in earlier validation studies from LMIC), 5% alpha error, and power of 80% [17].

Each eligible child underwent evaluation after obtaining written informed consent from the mother. Relevant study specific demographic and clinical details were documented. The researcher administered each index tool to the mother in no particular sequence followed by items of DP-3 (without scoring). The comprehensive assessment was performed by neurodevelopmental experts with 15-20 years of experience within a week. This included parental interview, observation of the child, review of videos of play, social interaction and repetitive activities at home (which the parents were asked to make at enrollment), computation of SS and GDS from the DP-3 records, and application of the DSM-5 diagnostic criteria for ASD. Administration of the index tools were repeated by the researcher in 20 mother-child dyads (10% sample size), and by the expert in 20 different mothers, selected as per convenience both within a week of initial screening.

Statistical Analysis: We used Statistical package for social science (SPSS) software version 28. Parameters of diagnostic accuracy (sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio), convergent validity (using spearman correlation coefficient), test-retest and inter-rater reliability (by intra-class correlation coefficient) were computed.

RESULTS

We assessed 224 children out of which 24 were excluded and 200 were enrolled as depicted in **Fig. 1**. The mean (SD) age of the study population was 22.7 (4.2) months; with boy to girl ratio of 1.2:1. Most children belonged to the lower middle (50%) and upper lower (35.5%) socioeconomic class as per modified Kuppuswamy classification. Clinical pallor was detected in 112 (56%), wasting in 29 (14.5%), underweight in 16 (8%), and stunting in 25 (12.5%) children.

The number of children who screened positive according to M-CHAT-R/F, RBSK and TABC were 29 (14.5%), 32 (16%) and 31 (15.5%), respectively. Thirty one (15.5%) children had delay as per DP-3 GDS. Twenty one (10.5%) children were diagnosed as ASD based on the DSM-5 criteria. These included 13 boys and 8 girls, all of whom were low functioning (GDS < 70). We did not find any child < 24 months who failed to satisfy the criteria for ASD, but exhibited delay or dissociation in the socioemotional and communication domains of DP-3. Comprehensive assessment yielded ASD in 21 (10.5%) children while 179 children (89.5%) did not have ASD. The parameters of diagnostic accuracy, and correlation coefficients for convergent validity and reliability are given in **Table I**.

DISCUSSION

We conducted this study to assess the diagnostic accuracy of the Hindi versions of M-CHAT-R/F, TABC, and RBSK-ASQ. Though M-CHAT-R/F reports acceptable sensitivity and specificity in high income countries (HIC) and some LMIC [15,16], there was no published research from India. The primary validation of the Malayalam version of TABC was conducted in 2-6-year-old children from Kerala [9]. However, its accuracy in children less than 2 years (and hence the first screening age of 18 months) was undetermined. RBSK-ASQ had never been validated.

A sensitivity and specificity of >70% is considered to be an acceptable trade off when it comes to the diagnostic accuracy of any developmental or ASD specific screening tool for young children. That equates to a realistic but fair balance between children incorrectly identified as false positive or false negative ASD. However, children who are screen positive but eventually get an alternative

WHAT THIS STUDY ADDS?

- The overall sensitivity and specificity of Hindi versions of M-CHAT-R/F was 95.2% and 94.4%; TABC was 100% and 94.4% and RBSK- ASQ was 100% and 93.9%, respectively.
- All three tools had high convergent validity and excellent test-retest and inter-rater reliability.
- Hindi versions of M-CHAT-R/F and RBSK-ASQ satisfy the suitability criteria for screening tools for ASD in LMIC.

diagnosis benefit from the in-depth evaluation, establishment of diagnosis, and appropriate intervention. The strategy of administering a second screening at 24/30 months increases the likelihood of identification of ASD, if the diagnosis was missed at first.

All the three tools had acceptable psychometric properties. We performed an exhaustive literature search to compare our results with validation studies in comparable populations originating from LMIC. Those in which the reference tool used was not suitable (i.e., another screening tool used instead of a diagnostic tool or comprehensive assessment) were excluded. Only three papers were found; two for M-CHAT-R/F and one for TABC. The first was a hospital-based study of 110 apparently typically developing Indonesian children aged 18 to 24 months [18]. The reference tool was DSM-5 criteria and the sensitivity and specificity were 88.9% and 94.6%, respectively. The second was a community-based study of 6,712 asymptomatic children between 16-36 months from Turkey [19]. A combination of DSM-5 criteria and Autism Diagnostic Observation Schedule was used as the reference tool, and 100% sensitivity and 67% specificity was demonstrated. TABC was recently validated against Childhood Autism Rating Scale, second edition (CARS2) in 65 children aged 2 to 6 years with suspected autism [20]. The psychometric properties were: sensitivity 96.3%; specificity 81.6%; positive predictive value 78.8%; negative predictive value 96.8%; positive likelihood ratio 5.22; and negative likelihood ratio 0.045.

The high convergent validity of all three tools reiterates the similarity of content with the clinical construct of ASD, even in the early stages. Tsai et al found moderate correlation (r 0.63) in the convergent validity of M-CHAT-R/F with Childhood Behaviour Checklist in 1.5- to 5-year-old children from Taiwan [21], probably because the latter evaluates non-ASD behaviors as well. Both test-retest and inter-rater reliability were excellent in our study. Studies of test-retest reliability from Serbia and China reported good correlation, 0.81 and 0.76, respectively [22,23]. We were unable to find research on inter-rater reliability from LMIC. Comparable data for TABC and RBSK-ASQ were unavailable. Taking everything into consideration, M-CHAT-R/F and RBSK-ASQ satisfy the suitability criteria for ASD specific screening tool in LMIC (**Table II**). Though M-CHAT-R/F is not being used by CHW or para-professionals, it can be administered by anyone with an educational level of higher than sixth standard and extensive training is not required.

The diagnosis of ASD is clinical based on observation of the behavioral and developmental phenotype. We used comprehensive assessment as the gold standard that would

Table II Comparison of Index Tools as per for Suitability Criteria for ASD Specific Screening Tools in Low- and Middle-Income Countries (LMIC)

Parameters	*RBSK-ASQ*	*M-CHAT-R/F*	*TABC*
Time taken	3-5 min	3-5 min	3-5 min
Cost	Free	Free	Free
Availability	Online [10]	Online [11]	CDC, Trivandrum
Administrating personnel	RBSK team	Pediatricians/ clinical psychologists[a]	CHW
Areas where used	India	India & few LMIC	Only in Kerala, India
Psychometric properties (primary validation study)	Not done	Sensitivity 66.7.% & Specificity 99.5% [5]	Sensitivity 80% & Specificity 91.1% [9]
Validation in Indian population	Not done	Unavailable	Community based study in Kerala

ASD Autism spectrum disorder, CDC Child Development Clinic, CHW Community Health Workers, LMIC Low and Middle Income Countries, M-CHAT-R/F Modified Checklist for Autism in Toddlers, Revised with Follow-up, RBSK–ASQ Rashtriya Bal Swasthya Karyakram- Autism Specific Questionnaire, TABC Trivandrum Autism Behavioural Checklist

Note: [a]As per the LMIC suitability criteria, the tool can be administered by a CHW or a para-professional

also be suitable for children aged 16 to 30 months. Though DSM-5 criteria have not set any basal age for application, it is well recognized that identifying autistic features in younger children is more challenging compared to older ones. Indirect evidence can be inferred from the lower age limits set for standard diagnostic tools for ASD; two years for CARS-2, 18 months for Autism Diagnostic Observation Schedule, and four years for Autism Diagnostic Interview-Revised. Therefore, examination of the developmental profile was included for children between 16 and 24 months, a priori, in case any child failed to satisfy the DSM5 criteria (though all of them did). Double blinding of DP-3 was not possible due to logistic issues. Though the items of DP-3 were asked by the researcher who administered the index tools, we tried to minimize bias by scoring and interpreting the responses by the experts afterwards. The possible respondent bias that may have arisen due to the hospital-based setting was alleviated by the strategy used for recruitment i.e. including stable children whose mothers were interested in their children benefitting from universal screening and developmental assessment, and therefore considered reliable. The fact that the sequence of administration of the tools was not randomized may be considered a limitation due to possible information bias.

Our study provides robust scientific evidence to support the use of Hindi translations of three popular tools used for screening Indian children for ASD at 18 and 24/30 months. This means expanding the coverage of screening to a larger population i.e. Hindi speaking respondents, by cadres of health care personnel who routinely come into contact with apparently typically developing young children. Each tool is easy to administer, score and interpret, and requires minimal training. Successful community-based administration of RBSK-ASQ by paraprofessionals, TABC by CHW and M-CHAT-R/F by nursing staff [24, 25] dispels the mistaken belief that screening should be restricted to medical professionals.

The next logical step would be to conduct a multicentric, community-based validation study of these tools in similar populations using appropriately translated versions, and administered by CHW or para-professionals. If found acceptable, competent authorities may consider incorporation into the curriculum and pre-service training of all concerned genres of health personnel, and we may find ourselves closer to the ultimate goal of universal screening.

Ethics clearance: Institutional Ethics Committee, Lady Hardinge Medical College New Delhi; No. LHMC/IEC/Thesis/2019/95, dated Oct 28, 2019.
Contributors: SBM conceptualized the study; SBM, SS planned the design of the study; DM was the researcher; SBM and SS were the neuro-developmental experts; DM, SBM and SS were involved in collection and analysis of data; SBM and DM prepared the preliminary draft. All authors gave their intellectual inputs during critical revision and approved the final manuscript.
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SIMULUS - 9

9th Annual Conference of PediSTARS on Healthcare Simulation

Theme: PURSUE PERFECTION THROUGH SIMULATION

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STEP Workshop: 31st August 2024 (Simulation training in Emergency pediatrics)	Limited seats	3000	3500	**SPOT Registration is not applicable**
NeoSIM Workshop: 31st August 2024 (Neonatal Emergencies by Simulation)	Limited seats	3000	3500	
SNAP Workshop: 31st August 2024 (Simulation for nurses in acute pediatrics)	Limited seats	2000	2500	
SimWars for Adults: 31st August 2024 (Max. Group no.8 per group 4 members)	Registration as group is mandatory	4000/ per group	4800 per group	
SimWars for Pediatric & Neonatal: 31st August 2024 (Max. Group no. 8, per group 4 members)	Registration as group is mandatory	4000 per group	4800 per group	
Competency Based Skills Trainer Course for Medical Faculty Workshop (CBME) : 31st August 2024	Limited seats	5000	6000	
Simulus – 9 Conference: 1st September 2024	PediSTARS non-members	3000	4000	4500
	PediSTARS members	2500	3500	4000
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	Nurses	10000	12500	
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5. Dr. Pooja Nawathe (USA)
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8. Rajasri Seethamraju (UK)
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ORIGINAL ARTICLE

Prevalence and Predictors of Celiac Disease in Children With Constipation

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ABSTRACT

Objectives: To determine the prevalence of celiac disease and its predictors in children with constipation.

Methods: A hospital-based cross-sectional comparative study was conducted between November, 2018 to April, 2020. Children aged 1-12 years were screened for the presence of constipation as per ROME IV criteria and designated as cases. Age and sex matched healthy children with normal bowel habits were enrolled as comparison group. Participants underwent a detailed history and examination, and were screened for celiac disease by estimating serum anti-tissue transglutaminase IgA antibody levels (tTG-IgA). Upper gastrointestinal endoscopy and duodenal biopsy were performed in all participants who tested positive on screening (serum tTG-IgA ≥ 20 U/mL). The prevalence of celiac disease and associated factors were compared between the two groups.

Results: A total of 460 children (230 in each group) with mean (SD) age 64.08 (37.12) months were enrolled. Twenty-one (4.6%) children screened positive for anti tTG antibodies, among these 15 (75%) children had biopsy features suggestive of celiac disease (Marsh grade III). Children with constipation had significantly higher prevalence of celiac disease (5.65% vs 0.87%, $P = 0.004$) compared to children without constipation. Wasting and stunting were significantly associated with celiac disease in constipated children ($P < 0.001$).

Conclusion: Children with constipation and associated growth failure have a high prevalence of celiac disease.

Keywords: *Gluten enteropathy, Malabsorption, Risk factors, Tissue transglutaminase*

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INTRODUCTION

Constipation is a significant problem during childhood, and its reported prevalence varies between 1-30% worldwide [1]. Pediatric outpatient departments are frequented by children presenting with complaints of abdominal pain and constipation often categorized as a functional gastrointestinal disorder. Previously, constipation has been documented as one of the presenting features in children diagnosed with celiac disease, which is amenable to treatment [2]

Celiac disease (CD) is a chronic immune-mediated entero-pathy caused by ingestion of gluten-containing food, in genetically susceptible individuals resulting in immune-mediated mucosal damage in small intestine. Prevalence of celiac disease varies globally, with a pooled sero-prevalence of 1.4% in general population [3]. In India, the prevalence of celiac disease according to one community-based study is 1.04% [4], which is concordance with seroprevalence of the world population. Presenting symptoms of celiac disease vary according to the age; typical gastrointestinal symptoms and failure to thrive are common in children less than two years of age. While, in older children and adults, atypical, non-specific extra-intestinal symptoms with few or no gastrointestinal symptoms are more common, such as abdominal pain, microcytic hypochromic anemia, osteoporosis, overweight, short stature, fatigue, depression and occasionally there is constipation, bloating, rectal prolapse or intussusception [5]. The timely evaluation of atypical symptoms can help in planning more focused strategies for early identification and timely management of underlying disease and thereby, reducing celiac disease-related morbidity, especially in developing countries [6].

Majority of the studies from India are related to typical manifestations of celiac disease in children. There is a concerning delay in diagnosis due to low awareness about the varied clinical presentation of celiac disease [7]. Recently, studies have reported a rise in the non-diarrheal presentation of celiac disease, and constipation as a presenting complaint has been documented in 1-31% of

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children diagnosed with celiac disease [8-11]. There is a paucity of data on the prevalence of the celiac disease in constipated children in developing countries, including India.

To address this knowledge-gap the current study was undertaken to estimate the prevalence of celiac disease and its predictors in children with constipation.

METHODS

This was a cross-sectional comparative study conducted in the department of pediatrics in a public sector tertiary hospital in Delhi, India, primarily catering to children belonging to urban low-income families of East Delhi and adjoining parts of Uttar Pradesh. An approval from the Institutional Ethics Committee–Human Research was obtained before the commencement of the study. Between November, 2018 and April, 2020, all children aged 1-12 years presenting to the outpatient department or emergency room with complaint of constipation were screened as per ROME IV criteria and enrolled [12]. Exclusion criteria comprised known case of celiac disease, those with a family history of celiac disease, hypothyroidism, those taking drugs causing constipation (antihypertensive drugs, antidepressants, oral iron supplementation, opiates and cannabinoids etc.), enteric myopathies or neuropathies, organic colorectal diseases, spinal cord injury and other central nervous system diseases, any surgical cause of constipation, chromosomal disorders, and chronic systemic illnesses. Age and sex matched healthy children (i.e children visiting outpatient department either with minor illnesses like upper respiratory tract infection, or for vaccination) with regular bowel habits were enrolled as comparison group.

Eligible children were enrolled after obtaining a written informed consent from the parent(s) or the caregiver for participation in the study. A comprehensive bowel history (passage of stools, straining, frequency, consistency, fecal incontinence, large fecal mass, feeling of obstruction etc.), along with relevant demographic and clinical history (including dietary, immunization, family and socio-economic history) was documented in a predesigned performa. Clinical exami-nation findings and baseline anthropometric parameters (weight, length, mid-upper arm circumference and head circumference) were recorded as per standard techniques.

All enrolled participants underwent baseline complete blood count and thyroid function tests. Celiac disease screening was performed by estimating serum anti-tissue transglutaminase IgA (tTG-IgA) antibody levels. Commercially available enzyme-linked immunosorbent assay kits (Xema-medica Co. Ltd., Moscow, Russia) were used for estimation; tTG-IgA levels >20 units/mL were interpreted as positive result of screening for celiac disease. Participants who screened positive, underwent upper gastrointestinal endoscopy (UGIE) followed by a duodenal biopsy [13]. Endoscopic findings such as absence of mucosal folds, scalloped mucosal folds, mosaic pattern of the mucosa between the folds in duodenum were suggestive of celiac disease. Biopsy specimens obtained from the bulb and the second or third part of duodenum were examined by histopathologist blinded to clinical history and graded using the modified Marsh grading [14]. Celiac disease was confirmed on the basis of Marsh grade III histopathological changes.

Children diagnosed with constipation were managed according to the standard guidelines including dietary modifications in the form of increased intake of dietary fiber and plenty of liquids, and medical management using laxatives or stool softeners [15]. Children with biopsy findings of celiac disease were counselled and started on gluten-free diet along with micronutrients supplements and kept in regular follow up. Those found to be anemic during examination were evaluated for type of anemia and started on iron / vitamin B12-folic acid supplementation.

To calculate the sample size, prevalence rate of prior study done by Sadjadei et al [16] was considered. With an estimated celiac disease prevalence of 6% in constipated children and 1% in healthy controls, a sample size of 210 children in each group was determined to be adequate to detect a similar prevalence rate in Indian children with 80% power and 5% levels of significance. To account for 10% potential loss, 230 children were enrolled in each group.

Statistical analysis: Data was analyzed with IBM SPSS Statistics Ver.25. Continuous data were summarized as mean (SD) while categorical data was expressed as in number and percentage. Differences between groups were calculated using an independent samples *t*-test for the normally distributed data and the Mann–Whitney *U*-test for data not normally distributed. Chi-square test was used for the comparisons of qualitative data. A multivariable logistic regression was performed for determining the predictors of celiac disease identified through univariate analysis ($P < 0.3$). $P < 0.05$ was regarded as statistically significant.

RESULTS

A total 460 (230 with constipation, 230 without constipation) children were included in the study; 229 and 230, respectively completed the study **(Fig. 1.)**. The mean (SD) age of the children was 64.08 (37.12) months, more than half of the participants were aged under five.

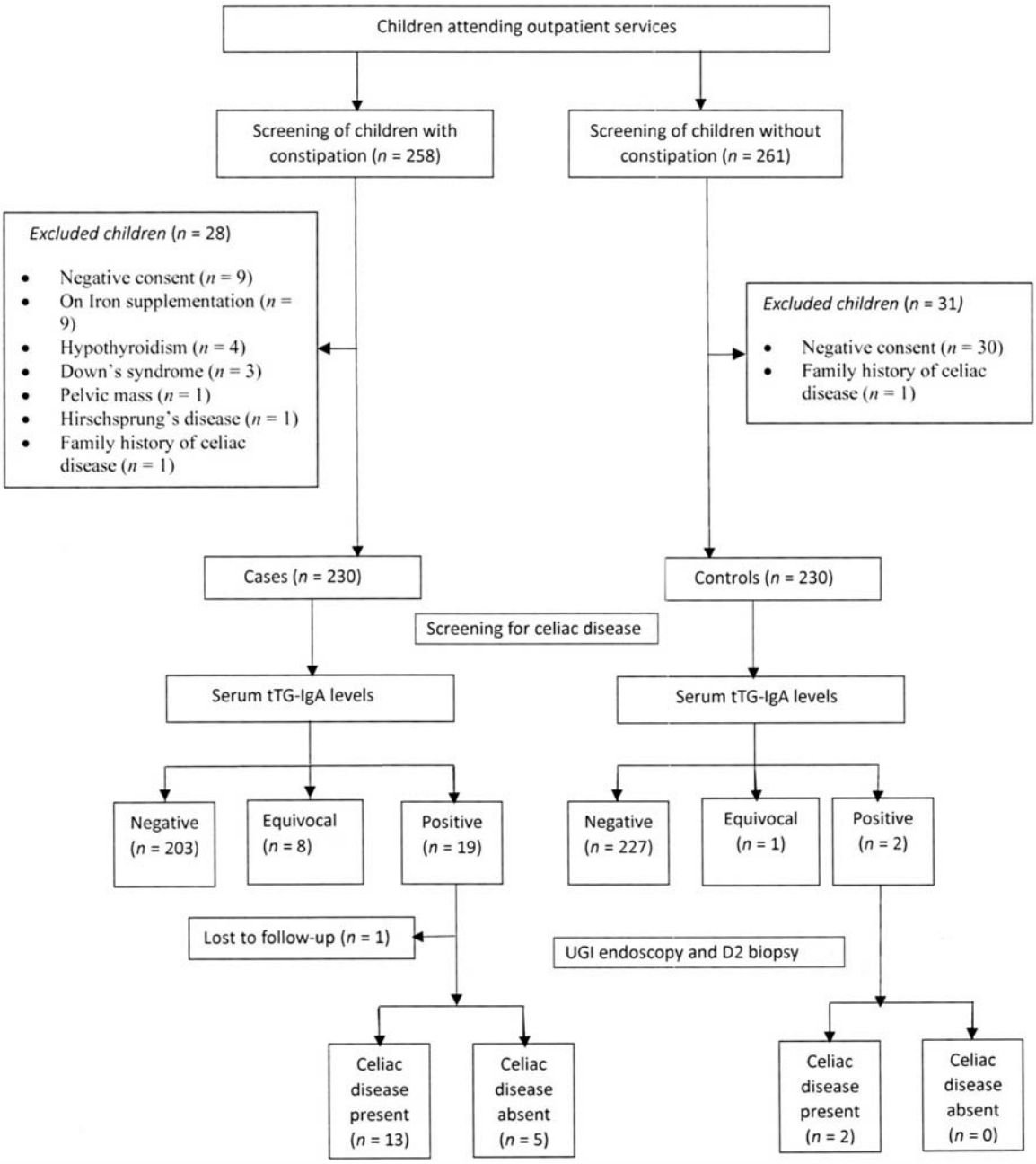

Fig.1 Flow of participants in the study

The children with constipation had a significantly lower weight for age, weight for height, body mass index and BMI z-score values in comparison to children without constipation. **Table I** depicts the comparison of the baseline parameters between two groups. On comparing the constipated children without celiac disease (n = 217) and children without constipation (n = 230), there was no significant difference in mean (SD) weight [16.76 (7.11) vs 17.86 (8.43) kg, P = 0.138] and height [104.85 (19.76) vs 104.93 (20.15) cm, P = 0.964], respectively.

Two hundred seventy (58.7%) children had anemia with mean (SD) hemoglobin level of 10.7 (1.6) g/dL; 7 (1.5%), 191 (41.5%) and 72 (15.7%) children had severe, moderate and mild anemia, respectively as determined using WHO defined cut-offs of hemoglobin for age. Peripheral smear examination for type of anemia showed predominantly normocytic normochromic picture in 381 (82.83%) children, while 77 (16.74%) children showed microcytic hypochromic RBCs, and 2 (0.43%) had a macrocytic blood picture. On comparing the two groups

Table I Comparison of the Baseline Characteristics of Children with Constipation (*n* = 230) and Children Without Constipation (*n* = 230).

Characteristics	*Children with Constipation (n = 230)*	*Children without Constipation (n = 230)*	*P value*
Male[a]	135 (59)	129 (56)	0.57
Age (mo)	63.74 (36.6)	64.43 (37.8)	0.84
Pallor[a]	60 (26.1)	5 (2.1)	< 0.001
Weight (kg)	16.61 (7.1)	17.95 (8.5)	0.07
Height (cm)	104.5 (19.7)	105.1 (20.2)	0.76
WAZ	-1.30 (1.04)	-0.95 (0.87)	< 0.001
HAZ	-1.09 (1.06)	-1.06 (0.55)	0.64
WHZ	-0.96 (1.17)	-0.46 (1.16)	0.001
Body mass index (kg/m^2)	14.65 (1.79)	15.36 (1.90)	< 0.001
BMIZ	-0.97 (1.20)	-0.47 (1.14)	< 0.001
Stunting[a]	25 (10.9)	7 (3)	< 0.001
Severe Stunting[a]	9 (4)	1 (0.4)	< 0.001
Wasting[a]	23 (10)	5 (2.2)	0.001
Severe wasting[a]	5 (2.2)	1 (0.4)	0.001

Values expressed as mean (SD), [a]n (%). BMIZ Body mass index z-score, HAZ Height for age z-score, WAZ Weight for age z-score, WHZ Weight for height z-score, mo Months

according to the severity of anemia there was no significant difference (*P* = 0.76). Results of thyroid function tests revealed a mean (SD) level of thyroid stimulating hormone were 3.34 (1.3) mIU/mL, while hypothyroidism was diagnosed in 1 (0.2%) child.

The mean (SD) value of serum tTG-IgA (U/mL) in the study participants was 8.33 (52.4); ranging from 0.1 - 838.8 U/mL. Twenty-one (4.6%) children screened positive for celiac disease and 9 (1.96%) children had equivocal results. There was a statistically significant difference in the mean (SD) serum tTG-IgA levels between children with constipation and those without constipation 13.2 (68.78) vs 3.5 (26.87), *P*=0.04), though the serum tTG-IgA levels were within the normal range. Out of 21 children who screened positive for tTG-IgA antibodies, 20 children underwent upper gastrointestinal endoscopy and biopsy. Among those undergoing UGIE and duodenal biopsy, 15 children (13 with constipation, 2 without constipation) had biopsy features suggestive of celiac disease (Marsh grade IIIa/ IIIb/ IIIc). There was a significant difference between the two groups, when the biopsy finding of celiac disease was compared the two groups (13 vs 2, *P* = 0.004). In our study, the proportion of celiac disease in constipated children was 5.65%; however, proportion of celiac disease in non-constipated group was 0.87%. In univariate analysis, presence of stunting in children with constipation was significantly associated with celiac disease (**Table II**). A significant association was found between presence of severe wasting, severe stunting and celiac disease among children with constipation (*P* < 0.001) (**Table III**).

DISCUSSION

The findings of present study suggest that there is a significantly high prevalence of celiac disease in children with constipation and growth failure than in children with normal bowel habits and it is more than the estimated prevalence in the population.

Celiac disease is a chronic immune-mediated enteropathy caused by ingestion of gluten-containing food, in genetically susceptible individuals. Mucosal inflammation and villous atrophy results in malabsorption presenting as diarrhea, abdominal distension and failure to thrive in majority of children. Disturbances in the gastrointestinal motility in untreated celiac disease patients

Table II Predictors of Celiac Disease in Children With Constipation (*n* = 230)

Parameters	*Children without celiac disease (n=217)*	*Children with celiac disease (n=13)*	*P value*	*OR (95% CI)*
Male gender	126 (58)	9 (69)	0.57	1.62 (0.48, 5.55)
Breastfeeding	214 (98.6)	13 (100)	0.55	1.00
Exclusive Breastfeeding	187 (86)	12 (92.3)	0.50	1.92 (0.24, 15.5)
Timely initiation complementary feeds at 6 months	176 (81)	9 (69)	0.29	0.52 (0.15, 1.78)
Anemia	130 (60)	8 (61.5)	0.91	1.07 (0.34, 3.38)
Wasting[a]	24 (20)	4 (50)	0.06	4.08 (0.95, 17.51)
Stunting	29 (13.3)	5 (38.5)	0.03	4.05 (1.24, 13.24)
Underweight	23 (23)	2 (40)	0.59	2.20 (0.35, 13.99)

All values in no (%), [a] Children <5 years (n=130)

WHAT THIS STUDY ADDS?

- The prevalence of celiac disease in children with chronic constipation and growth failure is higher than the general population.

Table III Predictors of Celiac Disease in Children With Constipation (*n* = 230)

Parameter	*Children with celiac disease (n =13)*	*Children without celiac disease (n =217)*	*P value*
Anemia	8/13 (61.5)	130/217 (60)	0.30
Moderate wasting[a]	2/8 (25)	21/122 (17.2)	< 0.001
Severe wasting[a]	2/8 (25)	3/122 (0.24)	
Moderate stunting	3/13 (23)	22/217 (10)	< 0.001
Severe stunting	2/13 (15.4)	7/217 (3.2)	

Values expressed as n (%), [a]n = 130 children aged <5 years

compared to controls have been reported. It has been hypothesized that immune mediated mucosal damage and inflammation may affect contractile gut motility through perturbations of the complex interactions among decreased food absorption, hormonal and neuro-immunomodulatory regulation of the intestinal mucosa. It is plausible that disturbed gastrointestinal motility may give rise to constipation in untreated celiac disease patients [17].

Previous studies examining the prevalence of celiac disease in constipated children have yielded diverse and inconsistent results. Studies from different regions have reported tTG-IgA seropositivity ranging from 1% - 50% [18–22]. Studies from Turkey, Iran, Colombia, USA and India have found no significant difference in the prevalence of seropositivity for celiac disease in constipated children as compared to general population [18,20–22]. In one of the largest series from India involving 316 children with constipation celiac disease was not reported as the cause of constipation [23]. In contrast studies by Sadjadei et al [16] (7.2%), Akman et al [19] (3.6%), Pelleboer et al [24] (1.8%) and Navarra et al [25] (51.2%) reported a significantly higher prevalence of celiac disease among constipated children than the general population, and these findings are consistent with the results of the present study.

Variability in participants' ethnicity, age group, inclusion and exclusion criteria, definition of constipation, sample size, cut-off values of tTG-IgA level, and histopathological staging discrepancies may have contributed to these differences. Some studies have included all consecutive children with constipation [22], while others have focussed on children referred to hospitals due to failed laxative therapies [16,23,24], creating discrepancies in participants' profile.

Only a few studies have assessed the anthropometric parameters while evaluating for presence of celiac disease in children with constipation. Similar to our study, Cakir et al [18] documented a significantly high prevalence of underweight and obesity in children with constipation comparison to healthy children (12.1% vs. 7.5%, $P < 0.05$, and 10.2% vs. 2.4%, $P < 0.05$, respectively) and Navarra et al [25] found high incidence of stunting in constipated children.

The main strengths of our study were that it tried to explore the prevalence of atypical symptoms (constipation) of CD among Indian children where childhood malnutrition is also common. Apart from this, presence of robust methodology with adequate sample size, minimal loss to follow up and confirmed diagnosis of CD by histopathology were some of the other strengths of our study. The main limitation was that it was a hospital-based study and hence the result obtained in this study might not be representative of the population in the community. Moreover, we were not able to perform biopsy in one child with constipation who was lost to follow-up Genetic testing was not performed in children diagnosed with CD. Also, we did not follow-up the CD patients after diagnosis to document the response to gluten-free diet and thus, are unable to comment on the effect of gluten-free diet on the requirement of laxatives and the cause-and-effect relationship between constipation and CD.

We conclude that there is a high prevalence of celiac disease in children with constipation, emphasizing the importance of considering atypical symptoms in the diagnosis of CD. Thus, routine serological screening among constipated children with growth failure as evident by the presence of stunting and wasting may help in the early diagnosis and treatment of CD, improving the quality of life, and reducing the long-term mortality and morbidity.

Ethics approval: Institutional Ethics Committee-Human Research (IEC-HR) of University College of Medical Sciences, Delhi, No. IEC-HR/2018/36/112, dated Oct 15, 2018.

Contributors: MN: Conceptualization, supervision of data collection, statistical analysis and interpretation, critical inputs to

manuscript writing; MM: Data collection and writing the initial draft of manuscript; RKM: Statistical analysis and interpretation, writing the initial draft of manuscript and editing the final manuscript; AA: Supervised data collection and its interpretation, critical inputs to manuscript writing. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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ORIGINAL ARTICLE

Renal Adverse Effects of Tenofovir Containing Regimens in HIV-Infected Children and Adolescents in North India

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ABSTRACT

Objective: To study the prevalence of abnormal renal functions among children living with HIV (CLHIV) receiving tenofovir disoproxil fumarate (TDF) containing antiretroviral therapy (ART).

Methods: A prospective, observational study was conducted among CLHIV aged 10 years to 21 years attending the pediatric HIV clinic. We included CLHIV weighing ≥ 30 kg who had been receiving TDF-containing regimens for at least 6 months, with estimated glomerular filtration rate (eGFR) > 60 ml/min/m^2 at enrolment and for whom baseline laboratory parameters were available before starting ART. Clinical and laboratory parameters like serum creatinine, serum phosphate, urinary protein and glucose estimation, CD4 count and viral load were noted from records. The mean change in serum creatinine, estimated glomerular filtration rate (eGFR), creatinine clearance, serum phosphate, and presence of urinary glucose and protein by dipstick were assessed at 3- and 12-months follow-up.

Results: We enrolled 70 patients with mean (SD) age 14.99 (2.45) years who had been receiving TDF-based ART for a mean (SD) duration of 14.60 (12.80) months. At 3-months and 12-months follow-up, 32.85% and 41.42% patients, respectively, had eGFR below 90 mL/min/1.73m^2, while 4.2% and 2.8% patients, respectively, had eGFR between 50-60 mL/min/1.73m^2. One patient had creatinine clearance below 50 mL/min/1.73m^2. Four patients had hypophosphatemia at the first and last follow-up respectively, and five patients had proteinuria. There was no statistically significant change in CD4 counts, serum potassium, or serum uric acid during study duration.

Conclusion: TDF-containing ART regimen is associated with decreased eGFR, creatinine clearance and proteinuria.

Keywords: *Antiretroviral therapy, Creatinine clearance, eGFR*

Trial Registration Number: CTRI/2022/09/045278

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INTRODUCTION

According to the India HIV Estimates Report 2020, the national adult (15-49 years) human immunodeficiency virus (HIV) prevalence was estimated at 0.22% in 2020; 0.23% among males and 0.20% among females. The national adult prevalence continued to decline from an estimated peak level of 0.54% in 2000-2001 through 0.33% in 2010 to 0.22% in 2020 corresponding to a 33.3% decline over the last 10 years [1]. The decline in HIV prevalence has been attributed to the use of robust antiretroviral therapy (ART) regimens and better screening and testing services. The U.S. Food and Drug Administration (FDA) has approved the use of tenofovir disoproxil fumarate (TDF) in children aged ≥ 2 years and weighing ≥ 10 kg when used as a component of ART [2]. TDF is an acyclic nucleotide analogue reverse transcriptase inhibitor (NtRTI) which is structurally similar to adefovir and cidofovir [3]. TDF is eliminated by the kidney through glomerular filtration and tubular secretion, and its clearance is in the proximal tubule of the nephrons and is controlled by active transport [4]. A high plasma concentration of TDF causes intracellular accumulation in renal tubular cells which increases the risk of renal toxicity.

Due to a long intracellular half-life, TDF allows for once-daily dosing and fosters treatment adherence with a better bioavailability [5]. TDF is recommended as the first line therapy in children living with HIV (CLHIV) [6]. The most common adverse effects of TDF are gastrointestinal symptoms and others include adverse effect on blood lipids, fat accumulation, and mitochondrial toxicity [7]. Systematic review and meta-analyses of randomized controlled trials and various observational studies have

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suggested that TDF-containing ART regimens are linked to a considerable loss of renal function [8]. Interactions between TDF and other anti-retroviral agents have been implicated in the development of renal toxicity [9]. Renal toxicity can manifest in the form of proximal or glomerular dysfunction, acute kidney injury, chronic kidney disease and end stage renal disease [10]. TDF-containing ART has shown to lead to a modest decline in renal function, more so in the initial 180 days of therapy, although the effect on estimated glomerular filtration rate (eGFR) was shown to stabilize between 180 and 720 days [11]. A decline in eGFR greater than 25% relative to baseline has been reported as ranging from 6 to 40.8% across different geographical locations of the world [12].

Limited studies are available showing TDF-related nephrotoxicity in the pediatric age group. A randomized trial in children receiving TDF as part of their highly active antiretroviral therapy (HAART) regimens reported a favorable safety profile [13]. Whereas, another pediatric cohort study from UK revealed renal toxicity especially with concurrent use of didanosine and lopinavir-ritonavir [14]. A case control study, in which serum renal function markers were determined in patients receiving TDF suggested a possible association between its use and development of hypophosphatemia [15]. A study from Africa reported a reduction in eGFR < 90ml/min/1.73m^2 in 35.9% of children receiving tenofovir disoproxil fumarate [16].

National AIDS Control Organization (NACO) guidelines recommend TDF based antiretroviral regimens as the preferred first line treatment of HIV in adults, adolescents, pregnant women and children in India [17]. To the best of our knowledge, there were no large observational studies in India assessing renal adverse effects of TDF containing regimens in CLHIV in India. So, this study was planned to assess the prevalence of renal dysfunction and its risk factors in CLHIV receiving TDF-containing regimens.

METHODS

A single-centre, prospective, observational study was conducted between August 01, 2021 to July 31, 2022, among CLHIV attending the pediatric HIV clinic of a tertiary hospital in North India to evaluate the renal adverse effects of TDF-containing regimens. All eligible CLHIV aged 10 years to 21 years or weighing ≥ 30 kg who had been receiving TDF-based ART for at least 6 months, with eGFR more than 60 ml/min/m^2 and whose baseline parameters were available before starting ART treatment were enrolled. Children with history of hypertension, diabetes mellitus, congenital heart disease, chronic liver failure, cardio vascular disease, nephrotic syndrome or hepatitis B and C infection or those whose care was transferred to another medical facility for logistic reasons were excluded. A written, signed and informed consent was obtained from the adult participants/parents/ caretakers of all participants before enrolment. Oral assent was taken from children between 10-12 years in presence of parents/guardians and a written assent was obtained from children and adolescents aged 12-18 years. Approval was granted by institutional ethics committee for human studies. This research was registered with Clinical Trial Registry of India (CTRI).

There are no studies assessing the prevalence of renal dysfunction in children receiving TDF-based regimens from India. A case series from India found no renal adverse effects with the use of TDF in children [18]. Based on estimates provided by NACO [17], a prevalence of TDF-associated renal dysfunction was assumed as 5% [17]; a sample size of 73 children is needed at 80% power, α error of 0.05 and 95% confidence interval to ascertain the prevalence of renal dysfunction in CLHIV receiving TDF-based ART.

Baseline serum creatinine, CD4 count and viral load with clinical characteristics including age, and weight, height and body mass index (BMI) of selected patients were noted from hospital records. All participants were followed-up regularly at the HIV clinic every month for 12 months after enrolment. Serum creatinine, CD4 count, viral load, serum phosphate and urinary glucose and proteins were estimated at 3- and 12-months follow-up during the study period.

Blood glucose was measured by glucometer (my life Pura X) with measurement range from 10 to 600 mg/dL (0.6 to 33.3 mmol/L). Urinary protein and glucose was assessed by standard dip stick method (Siemens Uristix). Siemens Uristix has a urinary detection threshold of 15-30 mg/dL for albumin and 75-125 mg/dL for glucose.

CD4+ cell count was analysed with Sysmex Partec's CyFlow Counter System flow cytometer. CD4 count was assessed at 6 monthly intervals. Viral load testing for HIV-1 viral load was done by Taqman Plasma (Quantitative) using test principle of real time PCR.

Calculation of eGFR was done by simple height independent equation of 'Pottel' where eGFR = 107.3/ (Scr/Q), Q = 0.0270 × age + 0.2329 (age in years) and Scr is serum creatinine (mg/dL). Creatinine clearance was calculated by the 'Cockcroft-Gault equation' where creatinine clearance (CrCl) = {(140-age) × weight/ (serum creatinine × 72)} × 0.85 (if female), CrCl (creatinine clearance) in mL/minute, age in years, weight in kg and serum creatinine in mg/dL [19-21]. Serum phosphate was

graded from 1 to 4 according to the Division of AIDS (DAIDS) adverse events table [22]. TDF-associated renal alteration was defined by decrease of eGFR by > 25% from baseline [12]. Proximal tubular dysfunction was defined by hypophosphatemia as < 2.7 mg/dL, proteinuria as 1+ or 30 mg% on urine dipstick, glycosuria as at least 1+ or 30 mg% (in the presence of normal serum glucose), hypouricemia as < 2 mg/dL and hypokalemia as < 3.56 mEq/L [22,23].

Statistical Analysis: The data was tabulated and entered in Microsoft Excel and analyzed using SPSS version 23. The change in serum creatinine, eGFR, creatinine clearance, CD4 counts, and serum phosphate data were analyzed using Wilcoxon signed rank test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 70 patients (41 boys, 29 girls) aged 10 years to 19.5 years were included in the study. The mean (SD) age of participants was 14.99 (2.45) years. The body mass index (BMI) ranged from 15.06 kg/m^2 to 23.28 kg/m^2 with mean (SD) BMI of 18.00 (1.82) kg/m^2. The characteristics of the study participants at the time of enrolment are shown in **Table I**. The study selection process is illustrated in **Fig. 1**.

All patients were on TDF-based regimens at the time of enrolment. Most of the participants (48/70) had been receiving TDF-based ART for the past 6-12 months. Of the remaining, 11, 7, and 4 participants had received TDF-based ART for 12-24 months, 24-36 months, 36-72 months, respectively. The mean (SD) eGFR (ml/min/1.73 m^2) at enrolment was 106.71 (6.52). This decreased significantly by 13.1% to 92.75 (14.87) at 3 months follow-up ($P < 0.001$) and by 14.71% to 91.01 (14.77) at 12 months follow-up ($P < 0.001$) (**Fig. 2a**).

Table I Characteristics of HIV-Infected Children and Adolescents on Tenofovir (TDF) Containing Regimens at enrolment (*N*=70)

Parameter	*Values*
Male	41 (58.6%)
Female	29 (41.4%)
Age (y)[a]	14.99 (2.45)
Weight (kg)[a]	33.98 (3.68)
Height (cm)[a]	146.03 (10.58)
BMI (kg/m^2)[a]	18.00 (1.82)
Duration of TDF containing regimens (months)[a]	14.6 (12.80)
CD4 count (cell/mm^3)[a]	622.11 (304.90)
Serum creatinine (mg/dL)[a]	0.59 (0.16)
eGFR (mL/min/1.73m^2)[a]	106.71 (6.52)
Creatinine clearance (mL/min)[a]	93.94 (12.61)

Values are in *n* (%), or [a]mean (SD)
ART Antiretroviral therapy, eGFR Estimated glomerular filtration rate, TDF Tenofovir disoproxil fumarate

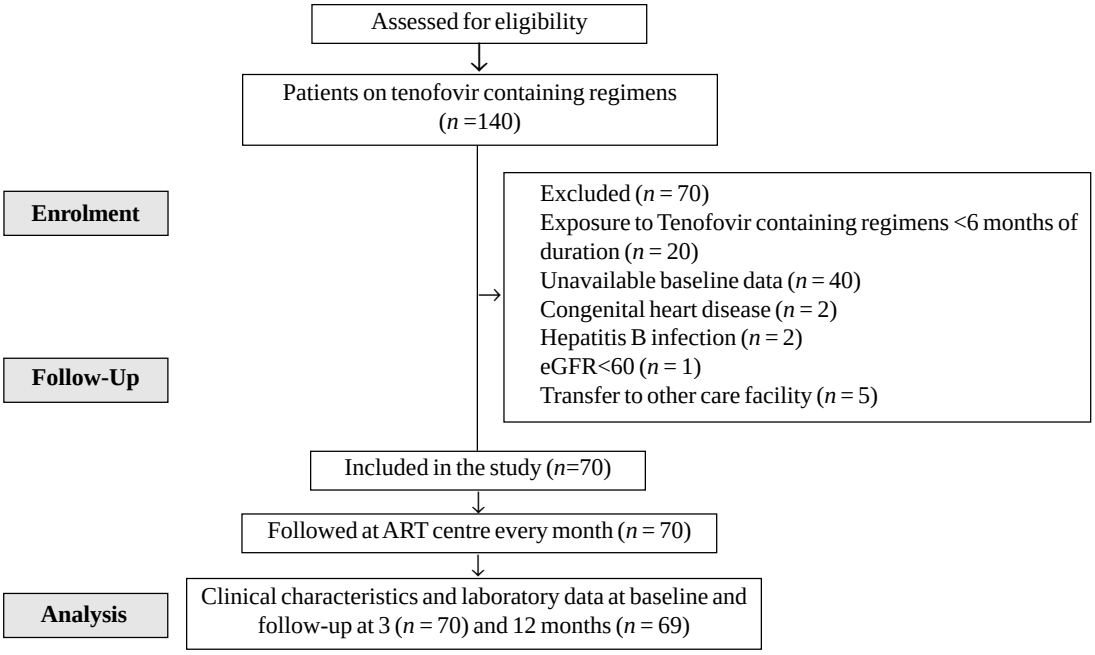


Fig. 1 Flow of participants in the study

A significant increase in serum creatinine of 26.85% was noted from enrolment; 0.5904 (0.16) to 0.7489 (0.14) at 3-months follow-up ($P < 0.001$). We found a significant increase in serum creatinine (mg/dL) of 32.91% from enrolment; 0.59 (0.16) to 0.78 (0.14) at 12 months follow-up ($P < 0.001$) (**Fig. 2b**). In our study we have found 4.28% and 7.14% patients had serum creatinine more than 1 mg/dL at 3-months follow-up and 12-months follow-up, respectively.

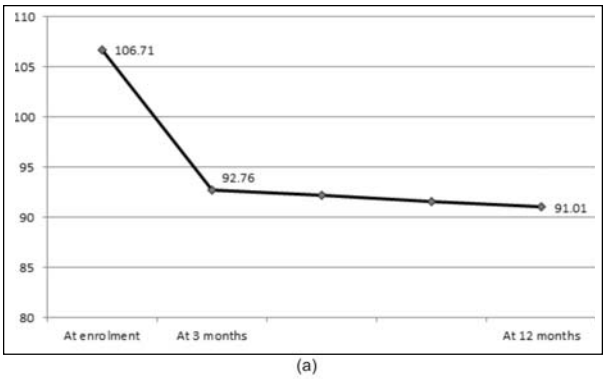
A significant decrease in mean (SD) creatinine clearance of 9.5% was seen from baseline 93.94 (12.61) to 85.04 (15.61) at 3-months follow-up ($P < 0.001$). We found a significant decrease in the mean (SD) creatinine clearance of 10.4% from baseline, 93.94 (12.61) to 84.20 (10.37) at 12 months follow-up ($P < 0.001$).

In our study creatinine clearance below 90 mL/min was seen in 60% participants ($n = 42$**)**, out of these 7.1% participants ($n = 5$) had creatinine clearance between 50 to 60 mL/min and 1.4% participants ($n = 1$) had creatinine clearance below 50 mL/min at 3-months follow-up (aged 18 years; duration of TDF containing ART: 19 months). Thus, only one patient had decreased creatinine clearance below 50 mL/min who was shifted to an alternate regimen without TDF as per the NACO Guidelines. Also, at the last follow-up at 12 months, creatinine clearance below 90 mL/min was seen in 47% participants ($n = 33$), out of these 11% participants ($n = 8$) had creatinine clearance between 50 to 60 mL/min. Our results suggest statistically significant decrease in creatinine clearance along with the duration of TDF treatment (Wilcoxon signed rank test) (**Fig. 2c**). 20% (14/70) patients had a decrease in eGFR by >25% from baseline at 12-months follow up.

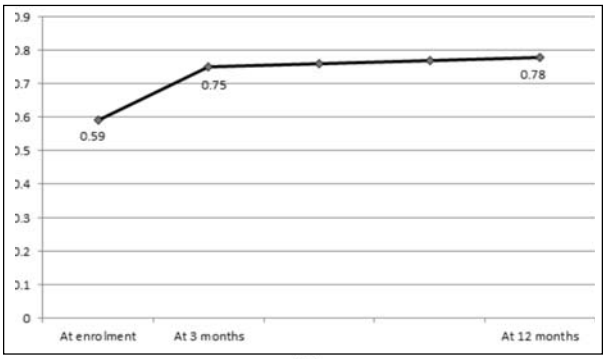
A decrease in mean (SD) serum phosphate of 5.23% was observed from the first follow-up [4.29 (3.76)] to [4.08 (0.76)] at the last follow-up ($P = 0.058$). Out of 70 patients, three patients had grade 1 and one patient had grade 2 hypophosphatemia at the first follow-up. At the last follow-up, one patient had grade 1 and three participants had grade 2 hypophosphatemia.

Proteinuria was not observed in any patient with treatment of TDF containing regimens during the study on first follow-up but at the last follow up 5 patients (7.1%) were having 1+ proteinuria. None of the patients developed glucosuria during this study on any follow-up.

A marginal decline ($P > 0.05$) in CD4 counts was observed in CLHIV on TDF-containing regimens at 3-months and 12-months follow-up; mean (SD) CD4 count at enrolment, 3-months and 12-months was 622.11 (304.90), 610.44 (232.96) and 577.44 (230.04) respectively.



(a)



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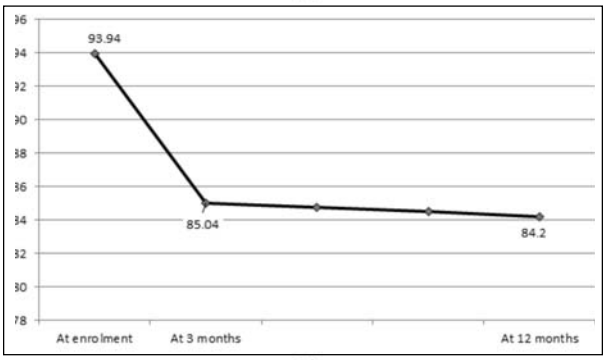

(c)

Fig. 2a Estimated eGFR (ml/min/1.73 m^2); 2b Serum creatinine (mg/dL); 2c Serum creatinine clearance (mL/min)

DISCUSSION

The WHO recommends that serum creatinine evaluation must be conducted before initiation of TDF and the patients with compromised renal function should not be started with TDF [2]. We observed that TDF containing regimens are associated with a significant decrease in eGFR, creatinine clearance and increase in serum creatinine values over follow up in North Indian HIV-infected children and adolescents.

A major limitation of our study is the heterogeneity in duration of treatment using TDF-based ART for all participants and the less duration of follow-up. Ideally, all children being started on TDF should be followed up on

WHAT THIS STUDY ADDS?

- Tenofovir-containing regimens are associated with a decreased eGFR, creatinine clearance and increase in serum creatinine values over follow up in North Indian HIV-infected children and adolescents.

same time points since commencement on TDF-based therapy. Besides, dietary factors, other medications and drug-drug interactions were not studied which may affect creatinine levels. Ours was an observational study from a single centre. The use of the Cockcroft-Gault formula is another limitation of the study. The strength of our study is that it enrolled largest number of HIV-infected children and adolescents from India.

We observed that TDF containing regimens are associated with a significant decrease in eGFR, creatinine clearance and increase in serum creatinine values over follow up in North Indian HIV-infected children and adolescents. All our patients on TDF containing regimens had normal renal function at baseline and had no pre-existing co morbidities. All study participants except one who was receiving TLD including the one who developed renal insufficiency were not previously on medications which could interfere or cause renal dysfunctions.

The mean decline in eGFR from baseline was statistically significant among our HIV-infected patients during all follow ups. This was consistent with the findings of another study among HIV-infected children [16] where in eGFR <90mL/min/1.73m^2 was noted in 35.9% of patients. In our study, eGFR below 90 mL/min/1.73m^2 was seen in 32.85% and 41.42% at the first and the last follow-up respectively. Previously, TDF has shown to impact the renal function in the initial 6 months of starting and the effect was shown to plateau thereafter [16]. Most of our participants had been on TDF-based ART for 6-12 months, implicating that continued decline in eGFR may occur even beyond 12 months of starting TDF warranting close monitoring of renal functions.

We observed that 4.2% (6/70) and 2.8% (4/70) patients had an eGFR below 60 mL/min/1.73m^2 at the first and the last follow-up respectively. A study by Vigano et al [25] observed a moderate reduction in renal function in underweight children. We observed non-significant hypophosphatemia from first to last follow-up which was similar to findings by Mashingaide-Mano et al [16]. We found urinary dip stick was positive for protein in 7.1% of participants. The prevalence of proteinuria was similarly reported in study of Mashingaide-Mano et al [17]. However, there was no occurrence of glycosuria during study period. Our study provides some evidence for TDF associated renal impairment in children and adolescents. We recommend more studies with longer follow-up to assess the same.

Ethics Approval: Institutional Ethics Committee, Medical College and associated hospitals; No.ECR/922/inst/UP/2017 I, dated July 01, 2021.

Contributors: RK, SAS, SKS: Collected the data, reviewed the literature and drafted the first version of the manuscript; MVS, SAS, MM: Conceptualized the study and revised the manuscript; NM, AS, RKY, RS, MS: Collected the data, reviewed the literature and statistical analysis; MVS, MM, SAS, AS: Critically reviewed the final version of submitted manuscript. All authors contributed to drafting of the manuscript and approved the final version of the manuscript; MVS: Shall act as guarantor of the paper.

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ORIGINAL ARTICLE

Occurrence and Severity of Deformational Plagiocephaly in Infants: A Single Center Experience

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ABSTRACT

Objectives: To estimate the occurrence and severity of deformational plagiocephaly among infants.

Methods: A hospital-based, cross-sectional study was done in the pediatric ward of a tertiary care hospital between April 1, 2022 to October 31, 2022. Cranial Vault Asymmetry Index (CVAI) and Argenta Clinical Classification were applied to consecutive infants aged 1 month to 1 year till the calculated sample size was achieved.

Results: 67 infants were recruited and the occurrence of deformational plagiocephaly in the sample was estimated to be 46.3%. Level 2 severity of deformational plagiocephaly was the commonest, while as per the Argenta classification, majority belonged to type I (39.2%). Male gender and developmental delay were the significant risk factors for plagiocephaly with an odds ratio (95% CI) of 3.73 (1.23, 11.26) and 19.25 (2.31, 160.3), respectively.

Conclusion: A high occurrence of deformational plagiocephaly was found in infants studied. There is a need for more studies to further corroborate these findings and study its associated factors.

Keyword: *Cephalometry, Cranium, Intellectual Disability, Prone position*

INTRODUCTION

Deformational plagiocephaly is a condition of cranial distortion leading to a flattening of the skull bones in infants attributed to an external molding force. Although deformational plagiocephaly is a type of cranial distortion and flattening, all kinds of cranial flattening are not deformational plagiocephaly [1]. For diagnosing this condition, various methods like anthropometry, imaging studies, and 3D reconstruction using computer software are available [2]. While craniometry is easier to perform and less resource-intensive, imaging studies and 3D reconstruction have proven more precise. However, in resource-constrained countries like India, imaging studies and 3D reconstruction are not routinely available or affordable, and very few centers offer the expertise needed, hence data on the deformational plagiocephaly among Indian infants is scarce. Extrapolating global data and findings on the Indian population is inappropriate owing to different demographics, risk factors, racial, cultural, and child-rearing practices. The global prevalence of deformational plagiocephaly amongst infants aged 1 month to 1year ranges from 6.8 % to 40.5% [3,4]. Some of the risk factors associated with deformational plagiocephaly are - antepartum (oligohydramnios, multifetal gestation); intrapartum (birth order, presentation at birth, mode of delivery, male gender, and premature delivery) and postpartum (torticollis, reduced tummy time, developmental delay) [3-5]. Traditional methods like massaging, pillow use, especially the ones with mustard seeds and repositioning are expected to reduce the incidence of deformational plagiocephaly [6].

Other than estimating the prevalence, there is also a need to categorize the infants based on the severity as measured by cephalometry. Severity assessment also helps in management as recommended by the Child Healthcare Organization of Atlanta (CHOA). Argenta Clinical Classification has been used as a reliable tool to evaluate cranial deformities and can even help predict the optimal duration of treatment [7]. The current study is aimed to determine the occurence and severity of deformational plagiocephaly among Indian infants and the risk factors for the same.

METHODS

A hospital-based study was carried out on infants aged 1months to 1 year admitted to the in-patient ward of the Department of Pediatrics of a tertiary care institute in Eastern India between April 1, 2022 and October 31, 2022. Infants with underlying conditions that could alter the

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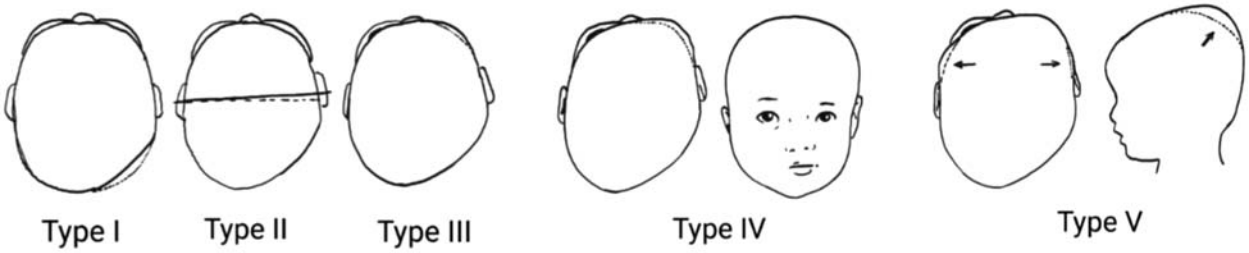
cranium shape, such as craniosynostosis, hydrocephalus, and sick infants were excluded from the study. Institutional Ethics Committee approval was obtained before the start of the study. Informed consent was obtained from parents after explaining the study details.

Based on a study from New Zealand wherein the prevalence of deformational plagiocephaly at 12 months of age was reported as 6.8% using craniometry [3], and assuming a prevalence of 5% in Indian children, at 95% confidence level and 5% margin of error, the sample size was calculated as 73.

A predesigned proforma was used to collect the demographic details including antenatal, natal, and postnatal history, as well as tummy time of infants. To avoid recall bias, documents like antenatal check-up records, vaccination cards, and ultrasonography reports were cross-checked. Tummy time was defined as an awake-prone position of a child supervised by an adult and was defined as "adequate" if at least three episodes of 10 minutes each or 30 minutes of total tummy time spread throughout the day while awake [8]. The developmental assessment was performed, and developmental delay was adjudged based on Trivandrum Development Screening chart. The developmental quotient was calculated for all infants participating in the study. Cephalometry was performed by the methodology described by Wilbrand et al [9]. Physical examination of the infant for identifying torticollis was done by assessing the active and passive movement of the head and checking sternocleidomastoid (SCM) tightness for a cord like feeling.

Cranial Vault Asymmetry Index (CVAI) was calculated by measuring the difference of the cranial diagonals (A and B, such that A>B) multiplied by 100 and divided by the longer cranial diameter A [9]. All measurements were done using a craniometer within the first 2 days of admission. All the measurements were obtained by a single person to avoid inter-observer variability. In a child with deformational plagiocephaly where there was an anterior ear shift on the side of the deformational plagiocephaly, the transverse diameter was recorded with the eurion being adjusted to the lateral most point on the temporoparietal region lying at a 90-degree angle to the AP diameter measured in line with the normally placed eurion of the opposite side. Based on the CVAI, the severity scoring was graded as, level 1 (< 3.5), level 2 (3.5-6.24), level 3 (6.25 to 8.74), level 4 (8.75 to 10.99), and level 5 (>11) [10]. Infants were classified as per the Argenta Clinical Classification by visually inspecting and clicking clinical photographs for each child (**Fig.1**). An infant was labelled as a case of deformational plagiocephaly only if he had CVAI ≥ 3.5, irrespective of the Argenta Clinical Classification of the infant.

Statistical analysis The collected data were analyzed using JAMOVI ver 2.3.18. Categorical variables were presented as frequency and percentage while the continuous data was presented as mean (SD). Fisher exact or *Chi*-square test was applied to examine the significance of association. Logistic regression analysis was performed to ascertain the risk factors for deformational plagiocephaly and odds ratio (95% CI) were computed. *P* value < 0.05 was considered statistically significant.



Clinical Finding	Type 1	Type 2	Type 3	Type 4	Type 5
Posterior asymmetry	Present	Present	Present	Present	Present
Ear malposition	Absent	Present	Present	Present	Present
Frontal asymmetry	Absent	Absent	Present	Present	Present
Facial asymmetry	Absent	Absent	Absent	Present	Present
Temporal bossing or posterior vertical cranial growth	Absent	Absent	Absent	Absent	Present

Fig.1 Argenta clinical classfication

RESULTS

Out of 69 infants who were assessed for eligibility, two infants who were found to have craniosynostosis were excluded. Out of 67 infants, 31 infants (46.3%) had CVAI ≥ 3.5 and were labeled as cases of deformational plagiocephaly. The mean (SD) age at the time of assessment was 175 (97) days in the deformational plagiocephaly group and 168 (90) days in the non-deformational plagiocephaly group (*P*=0.74).

Out of 31 infants who were found to have deformational plagiocephaly, 20 infants (64.5%) had level 2 severity, 8 infants (25.8%) had level 3 severity, 2 infants (6.5%) had level 4 severity, and 1 infant (3.2%) had level 5 severity. Based on the Argenta Clinical Classification, 11 (16.4%) infants did not show any physical deformation. Out of the remaining 56 infants, 22 (39.2%), 13 (23.2%), 18 (32.1%), and 3 (5.4%) infants were classified as Argenta Type I, II, III and IV respectively. We did not find any infant with the Argenta Type V severity (**Fig. 1**). Overall, 56 infants (83.6%) were found to have posterior asymmetry, 34 infants (50.7%) were found to have malposition of the ear, 21 infants (31.3%) were found to have forehead asymmetry, and three infants (4.48%) were found to have facial asymmetry.

Amongst the various risk factors for deformational plagiocephaly, male gender was significantly associated with developing deformational plagiocephaly (OR 3.73, *P* = 0.01) (**Table I**). Developmental delay was observed in 12 infants, and 11 (91.7%) among them had deformational plagiocephaly (OR 19.25, *P* < 0.01). There were 9 boys who had developmental delay and deformational plagiocephaly. There was no significant association observed between parity, mode of delivery, presentation at delivery, oligohydramnios or preterm delivery with deformational plagiocephaly as shown in **Table I**. Though reduced tummy time is seen in 91% of infants, we did not find any significant association between reduced tummy

Table I Risk Factors and Deformational Plagiocephaly

Factors	*Group*	*n (%)*	*Deformational Plagiocephaly*		*Odd's Ratio (95% CI)*	*P value*
			Present	*Absent*		
Gravida	Primigravida	32 (47.8)	18	14	2.17 (0.82-5.79)	0.12
	Multi-gravida	35 (52.2)	13	22		
Parity	Nullipara	39 (58.2)	20	19	1.63 (0.61-4.35)	0.33
	Multipara	28 (41.8)	11	17		
Oligohydramnios	Present	7 (10.5)	4	3	1.69(0.35-8.24)	0.51
	Absent	59 (88.5)	26	33		
	Not Known	1 (1.5)	1	0		
Type of gestation	Multifetal	3 (4.5)	1	2	0.56 (0.05- 6.57)	0.65
	Single	64 (95.5)	30	34		
Presentation at Birth	Vertex	26 (38.9)	12	14	NA	NA
	Breech	1 (1.5)	1	0		
	Not Known	40 (59.7)	18	22		
Mode of Delivery	Normal vaginal delivery	35 (52.2)	16	19	0.95 (0.36-2.5)	0.92
	Cesarean	32 (47.8)	15	17		
Preterm Delivery	Preterm	14 (20.9)	7	7	1.2 (0.37-3.93)	0.75
	Term	53 (79.1)	24	29		
Gender	Male	44 (65.6)	25	19	3.73 (1.23-11.26)	0.02
	Female	23 (34.4)	6	17		
Torticollis	Present	5 (7.5)	3	2	1.82 (0.28-11.67)	0.52
	Absent	62 (92.5)	28	34		
Reduced Tummy Time	Reduced	61 (91)	27	34	0.39 (0.07-2.33)	0.29
	Normal	6 (9)	4	2		
Developmental delay	Present	12 (17.9)	11	1	19.25 (2.31 -160.3)	< 0.01
	Absent	55 (82.1)	20	35		
Traditional Method usage	Yes	37 (55.2)	13	24	0.36 (0.13 - 0.98)	0.04
	No	30 (44.8)	18	12		

Data presented as n (%). DP Deformational Plagiocephaly, NVD Normal vaginal delivery

time and deformational plagiocephaly (**Table I**). The parents of 37 infants (55.2%) were using some traditional methods to maintain the cranial shape, which significantly reduced the occurrence of deformational plagiocephaly in our study (OR 0.36, and $P = 0.042$) (**Table I**).

DISCUSSION

The occurence of deformational plagiocephaly in our study was found to be 46.3%, which was higher than the 40.5% reported by Rocco et al [4] in the same age group and much higher than the 6.8% reported by Hutchison et al [3] in one-year-old children. There is great variability in the actual prevalence of deformational plagiocephaly in infants, which is dependent on the age at the time of assessment, tool and classification system used for evaluation. In our study, the mean (SD) age at the time of assessment was 171 (94) days and we have recorded a higher occurence as compared to that in studies where it is done within 8-12 weeks of age. Among the cases of deformational plagiocephaly, most infants (64.5%) had level 2 severity, followed by 25.8%, 6.5%, and 3.2% having level 3, 4, and 5 severities, respectively. Amongst the infants identified with plagiocephaly based on the Argenta Classification, most belonged to type I (39.2%), followed by type III (32.1 %), type II (23.2%), and type IV (5.4%). This differed from the findings of Branch et al [7] who found a maximum prevalence of type III followed by type II, type IV, type I, and type V. This may be because the study by Branch et al was a retrospective study among the infants presenting to a plastic surgeon for corrective surgery. Hence, infants with less severe type I may have been missed as they were self-limiting not requiring referral.

In our study, the significant risk factors for the development of deformational plagiocephaly were the male gender and developmental delay, with an odds ratio of 3.73 and 19.25, respectively. This was similar to the results observed by van Vlimmeren et al [6]. Though there is no concordance of risk factors associated with deformational plagiocephaly in infants in most studies but male gender and supine positioning have been associated in more than 50% of the studies [10]. We could not find any significant association of deformational plagiocephaly with parity. Similar results had been reported by van Vlimmeren et al [6] and Miyabayashi et al [11]. Unlike Solani et al [12], we could not find any significant association of oligohy-dramnios or multifetal pregnancy with deformational plagiocephaly. No significant association was observed between the mode of delivery or the type of presentation at birth in our study, similar to a study by van Vlimmeren et al. Assisted delivery has been believed to be associated with deformational plagiocephaly due to application of an instrument over the skull leading to a deformity. In our study, we could not obtain a history of assisted delivery, hence the results cannot be generalized for the same. A positive association between preterm delivery and torticollis with deformational plagiocephaly was observed in the current study though not statistically significant. This may be due to a small sample size. Preterm babies with softer skull bones may have a higher risk of positional deformity as compared to term babies [13]. Further prospective studies need to be designed specifically to look for the same in preterm babies. No significant effect of reduced tummy time was observed in developing deformational plagiocephaly in the current study which is in concordance with findings of van Ballardini et al [14]. Reduced tummy time was observed in almost 91% of our babies, which may be due to lack of awareness among parents. Traditional methods like massage, use of mustard pillow and repositioning were found to be beneficial for maintaining a normal cranial shape and hence may be recommended to parents. These traditional methods have been in practice for generations to stabilize the position of the head, which is considered one of the risk factors. Infants with positional preference of right or left during sleeping or feeding had four times higher risk of developing deformational plagiocephaly [15]. Infants with frequent change of head position while sleeping have lesser risk of having deformational plagiocephaly.

The strength of our study was the accurate measurements using a craniometer by a trained user. The limitations of the current study include a hospital-based set-up, a small sample size, the developmental assessment done in hospitalized children, recall bias and the lack of 3D cephalometry. Further prospective cohort studies are needed to ascertain the risk factors for deformational plagiocephaly.

Nearly, half of the infants in our study had deformational plagiocephaly; most cases were of severity level 2 by CVAI. Developmental delay and male gender increased the risk for deformational plagiocephaly, although parity, mode of delivery, presentation at birth, oligohydramnios and preterm delivery were not found to be associated with deformational plagiocephaly.

Ethics clearance: All India Institute of Medical Sciences, Bhubaneswar, Odisha; Institutional Ethics Committee No. IEC/AIIMSBBSR/STS/2021-2022/02 dated March 29, 2022.

Contributors: JJ: Conceptualized and designed the study, supervised the data collection and edited the manuscript; AKS: Supervised the data collection, did the statistical analysis and edited the manuscript; NKM: Collected the data, wrote the first draft of the manuscript and analyzed the results. All authors approved the final version of the manuscript.

WHAT THIS STUDY ADDS?

- The occurence of deformational plagiocephaly in our study was 46.3%, much higher than that reported globally.
- Male gender and developmental delay were the most significant risk factors for deformational plagiocephaly.

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ORIGINAL ARTICLE

Diagnostic Yield of Critical Sample and Elective Fast-Test in Children After a Hypoglycemic Event: Experience From a Single Center in Israel

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ABSTRACT

Objective: To determine the diagnostic yield of the critical sample and fast-tests as dynamic function tests for the work-up of hypoglycemia in children.

Methods: A retrospective record review of children (0-18 years) with a diagnosis of hypoglycemia (glucose ≤ 50 mg/dL) was performed. A comparison of results of critical sample (obtained during an episode of hypoglycemia) and fast-test (performed to induce hypoglycemia in fasting state) was done.

Results: In 317 patients with hypoglycemia, data of 89 critical samples and 52 fast-tests were taken. Only 7 (7.8%) patients who underwent critical sample testing received an endocrine or metabolic diagnosis. No confirmatory diagnoses were made using the fast-tests. Idiopathic ketotic hypoglycemia was detected in 33/89 (37.1%) of critical samples and 21/52 (40.4%) of fast-tests. The completeness of workup including the hormonal and metabolic profile was <80% in both tests.

Conclusion: The confirmatory yield of critical sample was better than fast-test. The processing of metabolic analytes was incomplete in a few, suggesting the need to rationalize the dynamic function testing.

Keywords: *Evaluation, Hyperinsulinism, Management, Urinary ketones, Idiopathic ketotic hypoglycemia*

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INTRODUCTION

Hypoglycemia in children is a common phenomenon [1], with hypoglycemia of unknown etiology seen in approximately 1:1400 pediatric emergency department (ED) visits [2]. Untreated hypoglycemia is a major cause of morbidity and can cause irreversible brain damage [3]. The laboratory evaluation obtained as part of assessment of the etiology of hypoglycemia is known as critical sample [4-7]. These tests measure the hormones and metabolites involved in glucose metabolism. A consensus approach regarding the specific laboratory tests that should be included in the critical sample is lacking [4-7].

Several limitations have been identified for the collection of critical sample in daily practice [8-10]. The collection of a critical sample may get missed when glucose is administered to the child through oral or intravenous route before arrival to the hospital. The samples may not be taken appropriately during an observed hypoglycemia event in the hospital. Therefore, patients may require elective fasting during hospitalization to diagnose the etiology of hypoglycemia. There are limited studies on elective fast-test that report the normal reference ranges of different metabolites [11-13], and safety during fasting [11,14].

The purpose of this study was to determine the diagnostic yield of appropriately collected critical samples and fast-tests as a part of workup of hypoglycemia.

METHODS

This was a retrospective record review of all non-diabetic children (age 0-18 years) who had presented to pediatric ED at Soroka University Medical Center (SUMC) between January 2014 and December 2018, and had a diagnosis of hypoglycemia at discharge (ICD code E16.2). The records of children with hypoglycemia, defined as a glucose level of 50 mg/dL or below detected on glucose meters (Ascensia contour blood glucose monitoring system, Bayer), and with onset after the first 48 hours of life, were included. Children with hypoglycemia attributable to diabetes mellitus or non-

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organic causes (intoxication) were excluded. In addition, the records of patients where blood was processed for insulin, ammonia, and cortisol simultaneously as part of critical sample evaluation on a single day were also included. In the latter group, the documentation of acute hypoglycemia was cross-verified in the electronic file. Duplicate entries were removed.

Patients' data were obtained from the SUMC computerized database. The demographic and clinical information obtained from medical charts included gender, ethnicity, critical sample or elective fast-test, laboratory results and diagnosis at discharge.

The metabolites measured as part of work-up in the critical sample included blood pH, bicarbonate, ammonia, lactate, serum insulin, serum C-peptide, growth hormone levels, cortisol level, blood carnitine profile, acyl carnitine levels and free fatty acids, and urinary ketones and organic acids. Serum chemistry, plasma ammonia, lactate and ketones, and blood gas determination were carried out at the chemistry laboratory, SUMC. Serum insulin, C-peptide, and growth hormone, were measured by the Immulite 2000 Immunoassay System (Siemens) and cortisol was assayed by ADVIA Centaur XP Immunoassay System (Siemens) at the endocrine laboratory. The coefficient of variance (CV) range for insulin was between 4.1-7.3%. Urine ketone estimation was performed bedside by urine dipsticks (Arkray). Urine organic acids and blood acylcarntine profile were determined by gas chromatography/mass spectrometry (GC/MS) and tandem mass spectrometry, respectively, at the metabolic laboratory of Hadassah Medical Center in Jerusalem. Idiopathic ketotic hypoglycemia (IKH) was diagnosed in the presence of positive ketones with normal levels of other metabolites on critical sample, and as per clinical judgement.

An elective fast-test was conducted in patients who did not complete a critical sample testing as per consultation with a pediatric endocrinologist. The duration of fasting varied according to the patient's age, ranging from eight hours for children younger than 6 months to twenty-four hours for children older than 7 years [14]. Critical sample was taken if the patient experienced a hypoglycemic event during the fasting period or at termination of the fast-test even if the glucose level was normal.

Statistical analysis: Data were analyzed using SPSS 18.00 software (SPSS Inc). Univariate analyses were conducted using a two-tailed Chi-square test for proportions or Mann-Whitney U test for continuous data, as appropriate. *P* value less than 0.05 was considered statistically significant.

RESULTS

The electronic files of 365 patients were reviewed out of which 317 (86.8%) were included. Of these, 176 patients were not evaluated by a critical sample or fast-test for various reasons viz., a known etiology of hypoglycemia, patients with acute illness or other reasons (**Fig. 1**). The detection rate of IKH was 44.9% (40/89) in critical sample and 40.4% (21/52) in the fast-test group. A total of 141 dynamic function tests were conducted, 89 as critical samples and 52 after a fast-test. Among the fast-test group, 14 (27%) had hypoglycemia during or at the end of the test, but no endocrine or metabolic pathology was identified. In the critical sample group, taken during hypoglycemia, 7 (7.8%) patients were found to have an endocrine or metabolic pathology (**Fig. 1**). Four were diagnosed with hyperinsulinism (three with persistent hyperinsulinemic hypoglycemia of infancy and one with hyperinsulinism/hyperammonemia). Three were diagnosed with metabolic conditions viz., phosphoglucomutase deficiency, dihydrolipoamide dehydrogenase (DLD–E3) deficiency and low carnitine levels (one each).

Ninety-two (29%) patients were diagnosed with IKH; 33 were diagnosed after a critical sample (37.1%), 21 after a fast-test (40.4%), and 38 patients were diagnosed without a critical sample or fast-test. A comparison of clinical and laboratory features between critical sample and fast-test group is shown in **Table I**.

The proportion of samples sent accurately after both tests are shown in **Table II**. The rates of properly performed critical samples or fasting test according to the protocol and resulting in reliable results were low, ranging from 8.9% in the critical sample group to 13.7% in the fast-test group.

DISCUSSION

In this study, we found a low yield of the fast-test for a confirmed metabolic or endocrine etiology as compared to critical sample testing. This rate is similar to a rate of 6% in a previous study [8].

The most common cause of hypoglycemia in the pediatric population is IKH [2,7]. The rate of detection of IKH was comparable between the two methods in our study, with an overall rate similar to earlier studies [15,16]. A higher detection rate of IKH (63%) has also been reported [2]. It is possible that higher performance rates of the urine ketones test would have resulted in higher chances of detection of IKH. Alternately, a few patients with diseases such as glycogen storage disease type 6 and 9 can be misdiagnosed as ketotic hypoglycemia and instead get missed [17].

The proportion of accurately performed workup was below 80% for most of the analytes in both the tests, as also reported earlier [8]. This reduces the chance of

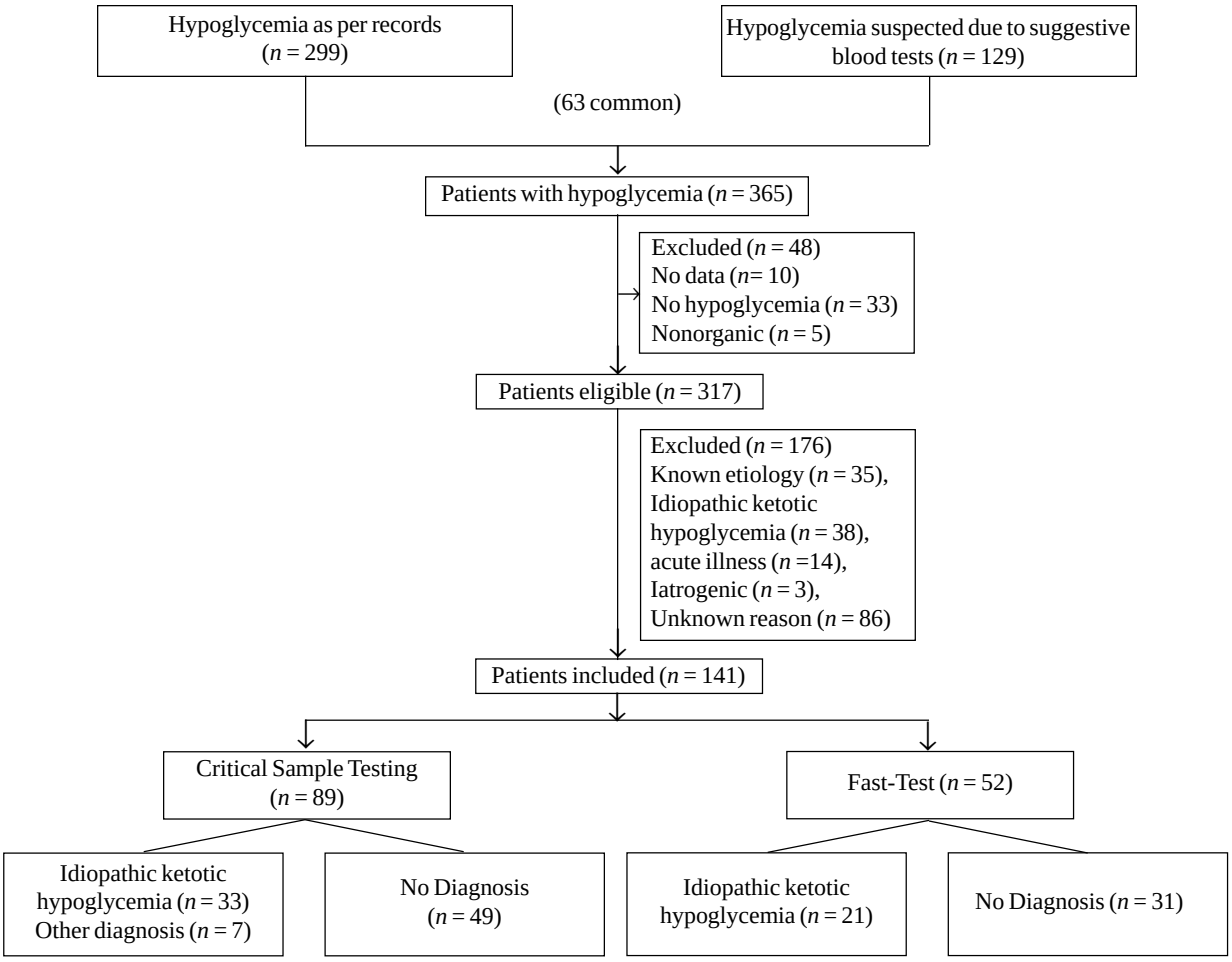

Fig. 1 Diagnostic yield of critical sample and fast-test in hypoglycemia

confirmatory yield on dynamic function testing in children with hypoglycemia. An earlier study reported a higher diagnostic yield (21.7%) during fast-test [14]. This difference may be a result of better patient inclusion (selection bias) [14], unlike the present study where selection criteria were not very robust. In both the test groups, samples for carnitine and acyl-carnitine, organic acid, free fatty acids and blood ketones were taken at lower rates, probably because of logistic difficulty in sample processing [8,10]. The missed opportunities during night shifts and holidays may explain the incomplete sample collection.

Table I Comparison of Critical Sample and Fast-test for Diagnosis of Hypoglycemia

Characteristics	*Critical sample*		*P value*	*Fast-test*		*P value*
	Diagnosis (n = 40)	*No diagnosis (n = 49)*		*Diagnosis (n = 21)*	*No diagnosis (n = 31)*	
Female sex	22 (55)	26 (53)	0.855	9 (42.8)	16 (51.6)	0.535
Age at presentation (mo)[a]	20 (10.5, 48.5)	4 (2, 16)	< 0.001	24 (13, 38.5)	34 (17, 54)	0.396
Jewish ethnicity	21 (52.5)	8 (16.3)	< 0.001	13 (61.9)	17 (54.8)	0.612
Previous event	7 (17.5)	8 (16.3)	0.883	2 (9.5)	7 (22.6)	0.222
Glucose (mg/dL)[b]	42.8 (9.89)	41.98 (10.72)	0.711	43.17 (9.57)	42.09 (10.55)	0.708

Values expressed as n (%), [a]median (IQR) or [b]mean (SD). Diagnosis inclusive of idiopathic ketotic hypoglycemia, hormonal or metabolic disorder

WHAT THIS STUDY ADDS?

- The confirmatory yield of critical sample was better than fast-test as dynamic function test in children with hypoglycemia.

Table II Comparison of Samples Processed for Different Analytes During Dynamic Function Tests for Hypoglycemia

Analyte processed	*Critical sample group (n=89)*	*Fast-test group (n=52)*
Insulin	64 (71.9)	41 (78.8)
C-peptide	60 (67.4)	34 (65.4)
Growth hormone	67 (75.2)	38 (73)
Cortisol	73 (82)	44 (84.6)
Ammonia	68 (76.4)	37 (71.1)
Lactate	69 (77.5)	41 (78.8)
Urine ketones	50 (56.1)	30 (57.7)
Carnitine profile[a]	43 (48.3)	35 (67.3)
Amino acid	45 (50.5)	29 (55.7)
Organic acid[a]	36 (40.4)	30 (57.7)
Free Fatty Acid[a]	30 (33.7)	27 (52)
Blood ketones	26 (29.2)	20 (38.4)

Data expressed as n (%); All parameters in blood except ketones; [a]P value <0.05

A major limitation of this study was reliability on point-of-care glucose testing to define hypoglycemia that is prone to inaccuracy [18]. The retrospective nature of the study limited access to information. The cost-effectiveness of the dynamic function was not evaluated.

To conclude, the performance of critical sample testing was found better than fast-test in determining a known metabolic etiology during dynamic function testing for hypoglycemia. Idiopathic ketotic hypoglycemia was the most common detected condition with similar yield on both tests. There is a need to rationalize testing for uncommon metabolites to improve detection and cost-effectiveness of the dynamic function tests.

Contributors: LC, RH: Contributed equally to the study conception and design, prepared the first draft of the manuscript; RH, MN: Material preparation and data collection; GH: Statistical analysis; EH, AH: Important intellectual contribution to study design and manuscript preparation. All authors gave critical inputs for revision, read and approved the final manuscript.

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ORIGINAL ARTICLE

Overweight and Blood Pressure in Pre-Pubertal Children: A Longitudinal Study

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ABSTRACT

Objectives: To analyze the longitudinal relationship between overweight and hypertension in school children.

Methods: This cohort study enrolled children 6-8 years of age who were then prospectively followed up over a 24 months period with repeat assessments performed at an interval of 11-13 months. Information on participation in physical education classes in school, sports practice outside of school, and economic status were obtained through questionnaires answered by parents/guardians. The measurement of blood pressure, weight, height, and waist circumference was performed during the serial follow-up visits in school.

Results: The proportion of hypertension did not change significantly over the 24 months (7.1% to 8.2%; $P = 0.690$). However, children with overweight and obesity throughout the period, had a 198% [HR (95% CI) 2.98 (1.40, 6.35)] higher risk of having hypertension diagnosed during follow-up when compared to eutrophic children in the same period.

Conclusions: The development trajectory of overweight and obesity in children aged 6-8 years was associated with hypertension.

Keywords: *Adiposity, Hypertension, Physical activity, Risk factors*

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INTRODUCTION

Cardiovascular diseases are the leading cause of death in adults worldwide, with more than three-quarters occurring in low- and middle-income countries [1]. Arterial hypertension, characterized by increased resting blood pressure, is one of the main cardiovascular diseases in adulthood [2]. In 2013, the prevalence of high blood pressure reached 15% in Brazilian children [3]. Hypertension tracks from early life to adulthood, increasing the risk of other cardiovascular diseases and early mortality [4].

Childhood obesity is one of the main determinants of high blood pressure in early life [5]. In 2020, 39 million children were diagnosed with obesity around the world [6]. The current understanding of the association between hypertension and childhood obesity is limited by a few cross-sectional studies in older children and adolescents [4,7]. The main objective of this study was to analyze the association between overweight and hypertension in 6 to 8-year-old children longitudinally.

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METHODS

This prospective study was carried out in the city of Presidente Prudente and was approved by the Ethical Board of the University of Western São Paulo. Presidente Prudente is in the western region of the State of São Paulo, Brazil and is characterized as the largest city in the region with about 200,000 inhabitants. The municipality administration (Department of Education) is responsible for running 29 primary schools in the city (grade 1 to 5) catering to children aged 6-11 years, that were invited to participate in the study.

The children aged 6-8 years were enrolled after an informed written consent from parents/legal guardians. Children were prospectively followed up at three time points, wherein measurements intervals ranged from 11 to 13 months, *viz* at August-December, 2016, 2017, and 2018. The research project was cancelled in 2019 during

the COVID-19 pandemic. All variables described below were measured at the aforementioned three-time points. The research team responsible for the anthropometric measurements comprised of two researchers, two physical education teachers, and two undergraduate students (pursuing the course of Physical Education) who were previously trained to take these measurements.

Blood pressure was measured by the auscultatory method, in accordance with the guidelines by the Brazilian Society of Cardiology [8]. Systolic (SBP) and diastolic (DBP) blood pressure were measured three times using sphygmomanometers (Premium brand, Hospitalar mesa/paredemodel). Measurements were obtained in the right arm, with the child in the sitting position, after a minimum of five minutes of rest (first measurement) by a trained team of seven undergraduate students. Hypertension was identified using the recommended cut-off points [8], which were adjusted for age, sex, and height percentiles.

Weight was measured on a digital scale (G-tech brand, Glass 10 model) with an accuracy of 0.1 kg, and height was determined on a wooden stadiometer with an accuracy of 0.1 cm, according to standardized procedures [9]. All measurements were recorded twice and a third observation was performed in case of discrepancy to adopt a mean value. Waist circumference (WC) was measured using a non-elastic tape with a 0.1 cm scale following standard procedure [9]. All measurements were performed with the children wearing light clothes (t-shirts and shorts/shorts) and barefoot. Considering percentiles adjusted for age and sex, overweight and obesity (Ow/Ob) were diagnosed when body mass index (BMI) values were ≥ 85th (overweight) and ≥ 95th (obesity) centiles, respectively [10].

Covariates considered in the statistical models, were sex, age, economic status, height, and sports participation. Economic status was assessed using a standard questionnaire completed by the parents/legal guardians [11]. Sports participation was reported by the parents/legal guardians considering the following question: "Over the past 12 months, was your child engaged in any sports activity, outside school and supervised by a professional (coach)?" [12]. Adherence to school physical education classes was also recorded.

Statistical analyses: Descriptive statistics consisted of mean values and standard deviation. Pearson correlation (*r*) was used to analyze the relationship between the numerical variables. The analysis of variance for repeated measures (ANOVA) compared numerical variables over the time of follow-up (adjusted by covariates). Associations were assessed by the Chi-square test and their magnitudes were expressed as hazard ratio (HR) and 95% CI by Cox regression (adjusted for sex, age, height, economic status, and sports engagement). *P* value < 0.05 was considered statistically significant. All analyses were run in the statistical software BioEstat (version 5.0, Tefé, Amazonas).

RESULTS

All the 29 schools were approached; of which 26 were willing to participate. Out of 1452 children whose parents/guardians were approached, 753 (51.5%) consented to participate in the study. The flow of the study participants is shown in **Fig. 1**. Sex distribution was similar in all stages of the study (Baseline: 280 boys and 298 girls; 12-months: 218 boys and 225 girls; 24-months: 132 boys and 124 girls). The general characteristics of the 256 children (132 boys, 124 girls) who completed follow-up over 24 months are presented in **Table I**.

The increase in WC and BMI were related to a significant increase in SBP and DBP, regardless of sex after adjusting for covariates (age at baseline, economic status, and sports engagement throughout follow-up) (**Table II**). As compared to children who were Not diagnosed with Overweight/Obesity during the 24-month follow-up, children with the presence of Overweight/Obesity in all assessments presented an increased risk of having hypertension (**Table III**). For each 1 kg/m² increase in BMI, there was an increase of 1.93 mmHg in SBP and 1.44 mmHg in DBP.

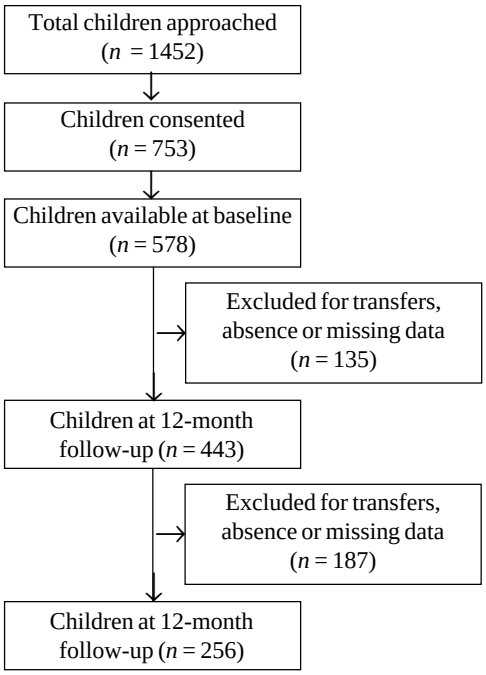

Fig.1 Flow of study participants during follow-up

Table I Characteristics of the Children who Completed Evaluation Over 24-months Follow-up (*n* = 256)

	Baseline	*12 months*	*24 months*
Chronological age[a] (y)	7.4 (0.6)	8.4 (0.5)	9.5 (0.5)
Body weight[a] (kg)	28.6 (7.7)	32.4 (9.2)	37.6 (11.2)
Height[a] (cm)	1.27 (0.06)	1.33 (0.07)	1.39 (0.07)
BMI[a] (kg/m^2)	17.3 (3.4)	17.9 (3.7)	19.1 (4.2)
WC[a] (cm)	59.7 (8.1)	62.2 (9.2)	65.6 (10.7)
SBP[a] (mmHg)	89.9 (9.9)	93.8 (10.2)	92.3 (11.6)
DBP[a] (mmHg)	57.9 (10.1)	61.5 (9.2)	61.3 (9.7)
Overweight[b] *n* (%)	89 (34.8%)	96 (37.5%)	118 (46.1%)
Hypertension, *n* (%)	18 (7.1%)	29 (11.3%)	21 (8.2%)
Sports participation, *n* (%)	55 (21.5%)	61 (23.8%)	62 (24.2%)
PE classes[b], *n* (%)	177 (69.1%)	222 (86.7%)	223 (87.1%)

Data expressed as mean and standard deviation (SD); BMI body mass index; WC waist circumference; SBP systolic blood pressure; DBP diastolic blood pressure; PE classes physical education classes [a]P value < 0.05 for analysis of variance for repeated measures (Baseline versus 24 months); [b]P value < 0.05 for Chi-square test (linear-by-linear association)

DISCUSSION

The present study showed an increased risk of developing hypertension in children with persistent overweight/obese status at 24 months follow-up. The prevalence of hypertension in this study was 7%, which is lower than that observed in Europe (22.8%) [13], Australia (12.6%) [14] and China (6.1 - 9.4%) [15]. This may be attributed to the sample of younger children in this study and other factors such as geographic factors, maturation, nutritional status, and level of physical activity [16].

BMI is an anthropometric index associated with hypertension, regardless of genetic, social, and geographic factors [5]. During follow-up in this study, children who were overweight/obese at baseline had a higher risk of hypertension during the follow-up. BMI is recognized as a determinant of blood pressure in pediatric age groups [17]. The association between obesity and hypertension relies on peripheral vascular resistance [4]. The peripheral vascular resistance attributed to obesity relies on sympathetic hyperactivity and insulin resistance generated by obesity, which decreases sodium excretion and impairs vascular reactivity [18]. Other indirect factors such as the presence of low-grade inflammation and the consumption of a diet rich in lipids, sodium, and sugars are also implicated [17,18].

Table II Relationship Between Changes in Anthropometric Indices and Changes in Blood Pressure Among Children

	Total (n= 256)	*Boys (n= 132)*	*Girls (n= 124)*
SBP			
BMI (kg/m^2)	1.93 (1.22, 2.65)	2.35 (1.44, 3.27)	1.21 (0.01, 2.42)
WC (cm)	0.61 (0.37, 0.86)	0.68 (0.38, 0.99)	0.50 (0.06, 0.94)
DBP			
BMI (kg/m^2)	1.44 (0.72, 2.16)	1.17 (0.21, 2.12)	1.91 (0.76, 3.06)
WC (cm)	0.41 (0.17, 0.66)	0.34 (0.03, 0.66)	0.61 (0.18, 1.03)

Values expressed as β (95% CI); model adjusted for age at baseline, economic status, and sport engagement throughout follow-up; All correlations were statistically significant at P value < 0.05
Model summary: SBP and BMI in boys r^2= 0.18 and girls r^2= 0.07; DBP and BMI in boys r^2= 0.05 and girls r^2= 0.09; SBP and WC in boys r^2= 0.14 and girls r^2= 0.08; DBP and WC in boys r^2= 0.04 and girls r^2= 0.07 BMI Body mass index; WC Waist circumference; SBP Systolic blood pressure; DBP Diastolic blood pressure

The association of physical exercise and blood pressure control is unclear in children [19]. Sports participation and physical education classes did not affect blood pressure in this study, similar to an earlier study in adolescents [20]. However, sports participation improves parasympathetic indices [20], in the absence of changes in blood pressure.

Table III Association Between Overweight/Obesity Trajectory Over 24 Months With Hyperytension

Ow/Ob Trajectory	*Hypertension detected on at least one of the assessments n (%)*	*Hazard Ratio (95% CI)*
Normal Wt (*n* = 129)	15 (11.6%)	1.00
New Ow/Ob on Follow-up (*n* = 9)	02 (22.2%)	1.91 (0.35, 10.36)
New Normal-Wt on Follow-up (*n* = 38)	07 (18.4%)	1.29 (0.46, 3.65)
Persistent Ow/Ob (*n* = 80)	28 (35.1%)	2.98 (1.40, 6.35)

Normal-Wt Normal-weight in all analyses, New-Ow/Ob Became overweight/obese at follow-up, New Normal-Wt No longer overweight/obese at follow-up, Persistent Ow/Ob Overweight/obese at all time points

WHAT THIS STUDY ADDS?

- An increased risk of hypertension was seen in young children (6-8 years) who developed or persisted to have overweight/obesity at the end of two years follow-up.

The limitations of this study include the fact that the volume and intensity of sports practice outside the school environment and school physical education classes were not measured. Additionally, sedentary behavior, diet, or parental history of hypertension, were not evaluated. We did not exclude a pre-existing diagnosis of chronic diseases and use of any regular medicines.

In summary, the prevalence of overweight/obesity prevalence increased significantly during the study period. This is concerning as overweight/obesity was shown to be linked to an increased risk of hypertension even in children aged 6 to 8 years of age over a two-year period.

Ethical clearance: The study was approved by the Ethics Research Committee of the University of Western São Paulo (UNOESTE [CAAE nº 51996615.0.0000.5515 protocol number 3008] dated March 23, 2016).

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ChatGPT in Pediatrics: Unraveling its Significance as a Clinical Decision Support Tool

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ABSTRACT

The integration of artificial intelligence in pediatrics holds transformative potential, reshaping healthcare through innovative approaches to diagnosis, treatment planning, and tailored clinical decision support. In the evaluation of ChatGPT's performance in pediatric case scenarios, the model displayed varying levels of proficiency suggesting the need for continuous refinement and collaboration with senior pediatricians for reliable pediatric decision support.

Keywords: *Artificial Intelligence, Chatbots, Child health, Medical Decision, Machine learning*

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Pediatrics presents distinctive challenges in healthcare, necessitating swift and precise decision-making to safeguard the well-being of pediatric patients. A diverse range of medical conditions including respiratory, cardiovascular, infectious, traumatic, and other acute illnesses, demand prompt attention and intervention across all age groups [1]. Management of such children requires specialized knowledge, rapid assessment, and tailored intervention considering their unique physiological and psychological needs [2]. Artificial intelligence (AI) has emerged as a transformative force in healthcare, contributing to advancements in diagnostics, treatment planning, and overall patient care [3]. Machine learning algorithms, natural language processing, and chatbot technologies, integrated into Clinical Decision Support Systems (CDSS), have empowered healthcare professionals with intelligent tools to aid decision-making [4]. AI technologies show promise in enhancing the efficiency and effectiveness of clinical interventions in pediatrics, where timely responses are crucial. ChatGPT, built on the GPT-3.5 architecture, can serve as a conversational AI model proficient in understanding and generating human-like text [5]. In the scope of child health, ChatGPT can function as a valuable CDSS, delivering real-time, context-specific information and guiding healthcare professionals. Its natural language understanding capabilities enable it to interpret clinical queries, review patient data, and provide evidence-based recommendations, thereby facilitating an informed decision-making [6]. This study aims to assess the potential of ChatGPT in providing medical diagnosis and management for diverse pediatric cases.

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ChatGPT – 3.5, a publicly accessible version was used for this evaluation. Twenty four clinical case scenarios were selected from "100 Cases in Paediatrics" by Cheung et al [7]. The cases were selected from various pediatric subspecialties including respiratory, cardiology, endocrinology and diabetes, gastroenterology, nephrology, infections, dermatology, hematology, oncology, orthopedics, neurology and psychiatry. In each of the subspecialties, two cases were used to converse with ChatGPT. The level and complexity of the cases included in the resource material were tailored to the knowledge and expertise of medical students and junior doctors. The generated responses on ChatGPT were cross-checked with the standard answers provided in the educational material and graded [7]. Grade A was awarded for responses that correctly matched with the key, Grade B for responses that needed improvement and Grade C was for responses that did not match with the key. The case queries included diagnosis, differential diagnosis, causes, complications, investigations and treatment strategies.

ChatGPT demonstrated varying levels of proficiency in addressing a spectrum of pediatric specialty case scenarios as shown in **Table I**. The scenario of congenital heart disease, cardiogenic shock, urinary tract infections (UTI), and bullous impetigo were graded as C for incorrect diagnosis of persistent pulmonary hypertension

Table I Grading of Pediatric Clinical cases in AI model using Chat-GPT

Pediatric Specialty	*Case Scenario*	*Grade Provided*
Respiratory	Stridor	A
	Acute Bronchiolitis	B
Cardiology	Congenital Heart Disease	C
	Cardiogenic shock	C
Endocrinology and Diabetes	Type 1 Diabetes Mellitus	A
	Marfan Syndrome	A
Gastroenterology	Pyloric Stenosis	A
	Viral gastroenteritis	A
Nephrology	Urinary Tract Infections (UTI)	C
	Nephrotic Syndrome	A
Infections	Measles	B
	Malaria	A
Dermatology	Scabies	A
	Bullous Impetigo	C
Hematology	Pancytopenia	B
	Idiopathic Thrombocytopenia	A
Oncology	Wilms Tumor	A
	Acute Lymphoblastic Leukemia	A
Bones and Joints	Juvenile Idiopathic Arthritis	A
	Scoliosis	A
Neurology	Epilepsy	B
	Viral Meningoencephalitis	A
Child Adolescent Psychiatry	Attention Deficit Hyperactivity Disorder (ADHD)	B
	Anorexia Nervosa	A

Grading based on accuracy of AI model for the case scenario according to the reference key

of the newborn, septic shock, acute pyelonephritis and Epidermolysis bullosa, respectively.

The varying proficiency levels demonstrated by ChatGPT in addressing pediatric case scenarios highlight both strengths and areas for improvement. When the model received a Grade A, it showcased an impressive ability to provide comprehensive information, covering clinical aspects such as diagnosis, differential diagnosis, causes, complications, investigations, and treatment strategies. In a few scenarios, where the responses were deemed acceptable, the model exhibited room for improvement. The inaccuracies in diagnosis could be the intricacies and nuances associated with these conditions, and potential overlaps in symptomatology that would have led to misdiagnoses. The model needs to undergo further training on these specific medical scenarios to improve accuracy.

The effectiveness of ChatGPT as a Clinical Decision Support System (CDSS) in Pediatrics lies in the provision of comprehensive information across various scenarios, serving as a valuable tool for clinicians seeking additional insights. However, the identified inaccuracies, in critical scenarios, underscore the need for caution when relying on ChatGPT for clinical decision support. The model's performance implies that it could serve as a useful supplementary resource but should not replace the expertise and judgment of healthcare professionals. AI algorithms like ChatGPT 3.5 and other Large Language Models will have to be primed with extensive resources and evaluated, before they may be effectively implemented as part of CDSS for senior pediatricians actual patient care. AI primed at this level should perhaps be only used by medical students and interns in pediatrics, with a caution to consult seniors before making final decisions.

A comprehensive program evaluation should be undertaken when implementing AI for the training of students and health care staff. This evaluation is crucial to assess the effectiveness, ensure accountability, refine the content based on feedback, improve patient-care outcomes, and adapt to evolving medical knowledge, to optimize the integration of AI into medical education.

ChatGPT is not yet ready to replace standard textbooks and guidelines and should be used with caution. There is a need for continuous refinement, validation, and collaboration between AI and healthcare professionals to enhance its reliability and safety. Adherence to established standards and updated guidelines is important for accurate diagnosis, appropriate investigations, and effective treatment in patient-care. While ChatGPT can provide valuable insights and assistance in healthcare, its reliance on pre-existing data and lack of real-time updates, warrants cautious use considering the medicolegal context.

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Trends of Publications and Country Rankings in Pediatrics, Perinatology, and Child Health from Asia: A Bibliometric Study from 1996 to 2022

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ABSTRACT

There is a need to analyze the trends of country-wise research output in child heath over the past few decades. A total of 7,87,812 global publications in pediatrics, perinatology and child health were found from 1996 to 2022 in SCOPUS, the largest abstract and citation database of peer-reviewed literature, covering over 35,000 journals from diverse disciplines. About 13.4% of these were published from Asia. There was an average growth of global publications of 3.53 times between 1996 and 2022, with China and India showing higher growth than the global average.

Keywords: *Asia, Child Health, h-index, Perinatology, Research*

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Research in pediatrics, perinatology, and child health is aimed to improve the overall health of children. The majority of research work in child health from Asian countries has focussed on neonatal care, infectious diseases, developmental disorders, vaccination strategies and adolescent health [1,2]. There is a paucity of global data or region-wise data in publication trends in child health. This study was conducted to analyze the productivity of research in pediatrics over the last three decades.

Bibliometric data of SCOPUS [3], was curated, from 1996 to 2022, and was evaluated on various bibliometric parameters. The quantitative assessment of data was based on the total number of publications by each country; whereas the qualitative assessment was done by citations, citations per document (CPD), h-index, and self-citations. In 1996, there were 15,695 publications in pediatrics, perinatology and child health recoded in SCOPUS database, with only 1,441 (9.18%) from Asia. In 2022, there was a leap in research output with 55,416 publications from all countries, and 10,776 (19.44%) from Asia. Between 1996 and 2022, 7,87,812 citable research papers in pediatrics, perinatology and child health were recorded in SCOPUS; of these 1,05,609 were from Asia (13.4% share) and 32,611 (4.1% share) from India. In terms of total research output between 1996 and 2022, United States of America was ranked one (30.1% share), followed by United Kingdom and Italy at rank two and three, respectively. India stood at the sixth spot and was the only Asian country amongst the top 10 countries in the world; Japan and China ranked 11 and 12, respectively in the global rankings. The comparative trend of global rankings of these three Asian countries over the years is shown in **Fig. 1.**

An average global growth in publication of 3.53 times was seen from 1996 to 2022 with three Asian countries showing a higher growth (China 262.13, South Korea 21.4, India 6.11 times) as compared to others. A qualitative assessment of the publications was done by assessing the h-index, citation per document (CPD), and self-citation rates [3]. Globally, United States registered the highest h-index of 476. Among the Asian countries, Japan had the highest h-index (126), followed by China and India (**Table I)**. Globally, Canada registered the highest average CPD of

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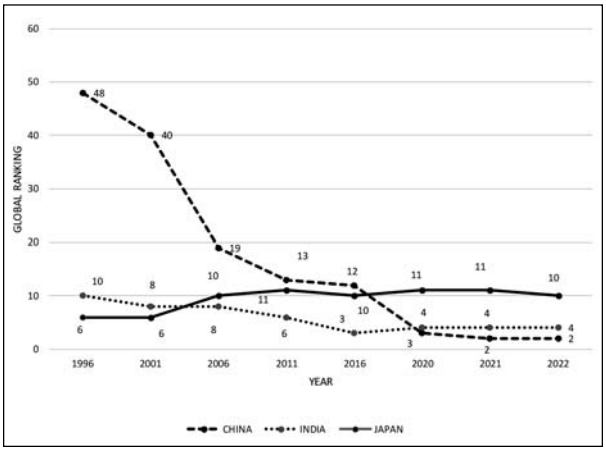

Fig. 1 Trend of Global Ranking of the top three Asian countries (China, India and Japan) in Pediatrics, Perinatology, and Child Health, from 1996 to 2022

Table I Bibliometric Profile of the top 10 Asian Countries in 2022

Country	*Documents (n)*	*Citations (n)*	*Citations Per Document (n)*	*Self-citations (n)*	*Self-Citation Per Document (n)*	*h-Index*	*Global Ranking*
China	3932	1685	0.43	788	0.20	110	2
India	2537	969	0.38	317	0.12	110	4
Japan	1584	657	0.41	197	0.12	126	10
South Korea	621	280	0.45	80	0.13	91	20
Taiwan	320	148	0.46	22	0.08	91	35
Thailand	282	126	0.45	24	0.08	65	36
Pakistan	227	88	0.39	23	0.10	60	39
Hong Kong	212	295	1.39	64	0.30	99	43
Indonesia	210	93	0.44	28	0.13	43	44
Singapore	202	184	0.91	11	0.01	66	45

Citations per document = Citations/documents; Self-citation per document = Self-citations/document

24.64, followed by the US, Australia and Germany [3]. Among the Asian countries, Hongkong had the highest CPD (19.74), followed by the Philippines (19.38). China and India had lower average CPDs of 7.01, and 5.50 respectively [3]. US had the highest self-citation per document (12.58), followed by the UK (5.33). Among the Asian countries, self-citations of publications was highest for China (2.36), followed by that of Japan (2.29), and India (1.98).

The contribution of Asian countries to the global growth in publication output has increased over last two decades with major contributions from China, South Korea, and India. While, India was the highest-ranking Asian nation till 2019, China emerged as a publication giant in 2020. The comparative trends of global ranking for the top three Asian countries demonstrate that China rocketed its global ranking only recently after the COVID-19 pandemic, whereas India and Japan have maintained/ improved their ranking, over the last three decades.

Substantial investments in research and development on STEM (science, technology, engineering, and mathematics) education has boosted China's recent growth [4,5], albeit with a few concerns about violation of publication ethics. It is pertinent to note that these numerics must be interpreted in the light of certain other factors like self-citation rates, quality of journals where the research was published/cited as well as retraction rates [6]. While India and China have the same h-index of 110, the self-citations for China are much higher [3]; h-index may have been skewed because of higher self-citations. The self-citations per document were higher in the US and UK, compared to the top Asian countries which indicates an apparent healthier publishing trend in Asia.

The publication trends also indicate that majority of research so far has been published from high-income countries and less from low-middle-income countries (LMICs) [3,7,8]. There is an urgent need for global collaborations to improve the understanding of health issues plaguing LMICs, like infectious diseases, malnutrition, and maternal mortality. This would allow for pooling of resources, funding, expertise, and advanced technology, that will help enhance the research output. It could also help in responding effectively to emerging global health threats, such as the COVID-19 pandemic [9]. The future of pediatric research in Asia holds great promise, provided there is continued investment in research, increased collaboration, integration of technological advancements, and a need for public-private partnerships [10].

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SPECIAL ARTICLE

Management of Urinary Tract Infections and Vesicoureteric Reflux: Key Updates From Revised Indian Society of Pediatric Nephrology Guidelines 2023

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ABSTRACT

Non-specific symptoms and difficulty in collecting urine specimens make the diagnosis of urinary tract infection (UTI) challenging in children. However, timely diagnosis and initiation of therapy are essential to prevent complications. Children with recurrent UTIs require detailed evaluation and follow-up for optimal management. We report key updates from the revised evidence-based practice guidelines of the Indian Society of Pediatric Nephrology for UTIs and primary vesicoureteric reflux.

Keywords: *Antibiotic prophylaxis, Children, Pediatrics, Recommendation, Vesicoureteral reflux*

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INTRODUCTION

Urinary tract infection (UTI) is a common bacterial infection in childhood affecting 1.7% of boys and 8.4% of girls before the age of 7 years [1]. UTI may be associated with acute discomfort, fever, and long-term complications such as hypertension and kidney scarring. The diagnosis of UTI in infants and young children is difficult. Primary vesicoureteric reflux (VUR) and bladder-bowel dysfunction (BBD) are the two most common risk factors for the recurrence of UTI. Almost 20-30% of children with the first episode of febrile UTI may have an underlying congenital anomaly, therefore prompt evaluation and treatment are important for managing acute and long-term complications associated with UTI. The last guidelines by the Indian Society of Pediatric Nephrology (ISPN) on this topic were published in 2011 [2]. In view of significant new evidence that has emerged in the last decade, the ISPN has recently revised and published evidence-based guidelines with robust methodology [3]. This article highlights the key updates in the recent guidelines (**Table I and Fig. 1**). **Box 1** describes the various definitions used in this review.

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METHODS

These guidelines were developed using international standards for the development of good-quality clinical practice guidelines. Initially six working groups and an evidence review group were formed. Thereafter, the groups developed questions in Population, Intervention, Control, Outcome, Methods (PICOM) format, performed a detailed systematic literature search, and used the GRADE approach to assess the quality of evidence and strength of recommendations [4]. While recommendations are based on evidence generated through systematic review and meta-analysis, clinical practice points are drafted chiefly based on limited literature or expert opinions. For detailed methodology one may refer to the original manuscript [3].

Salient Points

Diagnosis: The emphasis on urine dipstick for making a presumptive diagnosis of UTI

Diagnosis of UTI in children should be based on the significant growth of single uropathogens in urine culture in an appropriate clinical context. The presence of leukocyturia is not necessary. Growth of single bacterial species $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/mL) in urine obtained by suprapubic aspiration, catheterization, and clean-catch, respectively, is considered significant. The previous threshold of $\geq 10^5$ CFU/ml has been lowered in the present guideline due to many studies which suggest that true UTI may be missed with this strict definition,

Table I Summary of Key Recommendations and Clinical Practice Points (CPP) for the Management of Urinary Tract Infections and Vesicoureteric Reflux

T*opics*	*Description*	*Strength of Recommendation*[*]
Diagnosis		
CPP	The guidelines suggest using the clean-catch method for urine collection in toilet- trained children. For non-toiled trained stable children, clean catch should be attempted initially; if unsuccessful, the urine sample may be collected by catheterization or suprapubic aspiration.For sick infants, catheterization and suprapubic aspiration are the preferred methods for urine collection.	Not graded
Recommendation	The guidelines suggest using the urine dipstick (leukocyte esterase and nitrite combination) as a first-line screening test for UTI.	2⊕⊕OO
Recommendation	Urine microscopy (for bacteriuria and leukocyturia) in a freshly voided sample can be used as an alternative to the dipstick for screening of UTI.	2⊕⊕OO
CPP	Diagnosis of UTI should be based on positive urine culture in the presence of symptoms suggestive of UTI. The growth of single uropathogenic bacteria $\geq 10^3$, $\geq 10^4$, and $\geq 10^{4-5}$ (CFU/mL) in urine obtained by suprapubic aspiration, catheterization, and clean-catch, respectively, are highly suggestive of UTI.	Not graded
Treatment		
CPP	Antibiotic therapy should be initiated as early as possible, preferably within 48-72 h of the onset of fever.	Not graded
Recommendation	The guidelines suggest using 3rd-generation cephalosporins or amoxycillin-clavulanic acid as initial empirical antibiotic therapy in children with suspected febrile UTI.	2⊕OOO
Recommendation	The guidelines suggest first-generation cephalosporin (cephalexin, cefadroxil) or amoxycillin-clavulanic acid as initial empirical therapy in adolescents with cystitis.	2⊕OOO
Recommendation	Oral route is preferred over intravenous for administration of antibiotic therapy for treatment of acute febrile UTI in all patients except: (*i*) infants less than 2 months of age, (*ii*) severely ill patients, and (*iii*) patients who are unable to ingest oral antibiotic.	2⊕OOO
CPP	The guidelines suggest changing initial antibiotic therapy only in patients with clinical treatment failure regardless of antibiotic sensitivity patterns.	Not graded
CPP	The guidelines suggest 7-10 days of therapy with the antibiotic in children with acute symptomatic UTI.	Not graded
Recommendation	The guidelines recommend that 3-7 days of oral antibiotic therapy in children with cystitis.	2⊕⊕OO
CPP	Antibiotics should not be used for the treatment of asymptomatic bacteriuria. Urine cultures should not be performed in asymptomatic children.	Not graded
Imaging		
CPP	Ultrasound scan of the urinary tract should be performed after an episode of UTI in all children.	Not graded
CPP	The guidelines suggest performing micturating cystourethrography in children with one of the following: (*a*) UTI caused by non-*E.coli* uropathogens in children less than 2 years, (*b*) abnormal ultrasound scan, or (*c*) history of recurrent UTI.	Not graded
Recommendation	The guidelines suggest that an acute-phase DMSA scan should not be performed in children with febrile UTI.	2⊕OOO
CPP	Late-phase DMSA scan can be done to assess kidney scarring in children with recurrent UTI or high-grade VUR.	Not graded
Prevention of UTI		
Recommendation	The guidelines suggest against using antibiotic prophylaxis for prevention of UTI in patients with a normal urinary tract and absence of bladder bowel dysfunction.	2⊕OOO
Recommendation	The guidelines suggest using antibiotic prophylaxis for the prevention of recurrent febrile UTI in patients with high-grade (grades 3-5) VUR.	2⊕OOO
CPP	Antibiotic prophylaxis may be considered in preference to surveillance in patients presenting with recurrent febrile UTI and bladder-bowel dysfunction, irrespective of presence or absence of primary VUR.	Not graded

contd....

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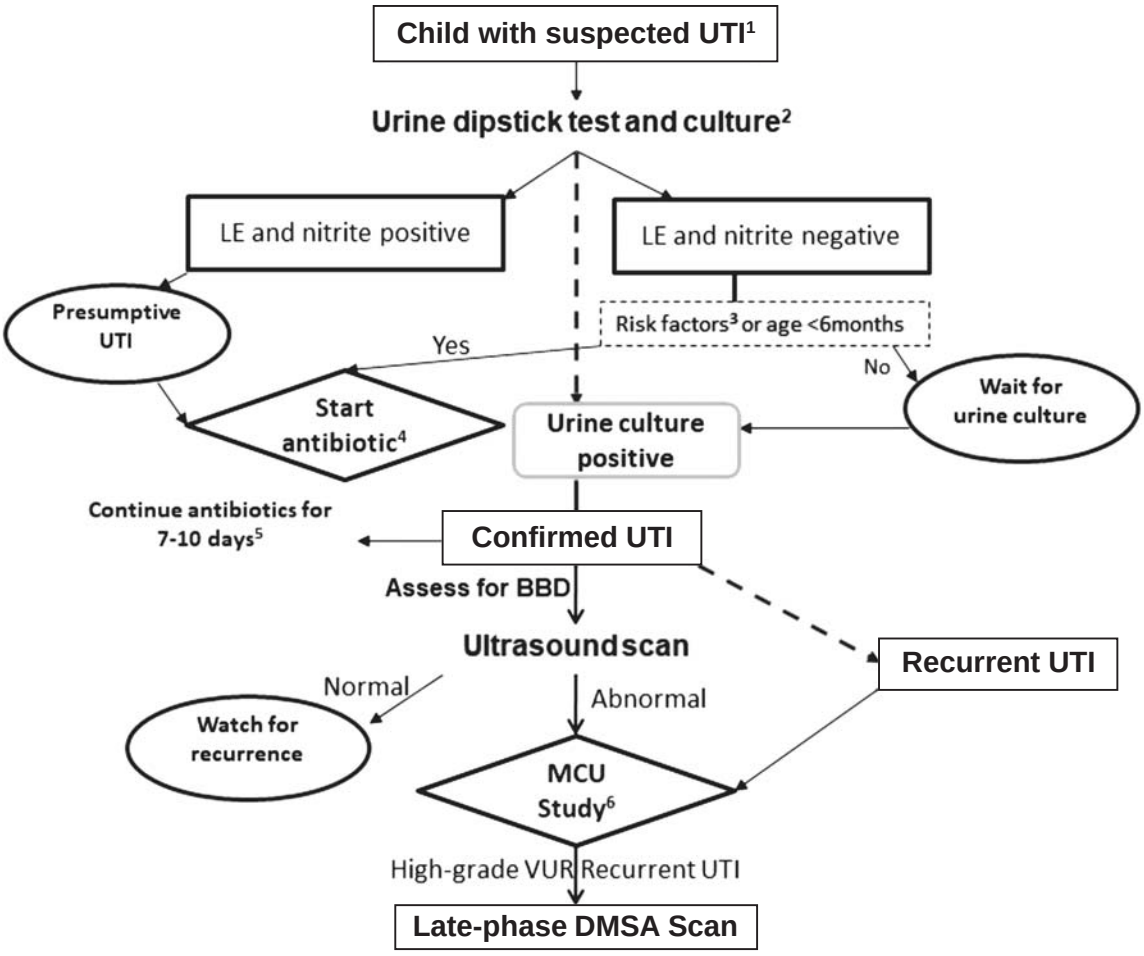
Topics	*Description*	*Strength of Recommendation*[*]
Recommendation	The guidelines suggest against using antibiotic prophylaxis for the prevention of symptomatic UTI in children with antenatally detected hydronephrosis while awaiting evaluation.	2⊕⊕OO
Recommendation	Cotrimoxazole or nitrofurantoin should be used as the first-line antibiotic for prophylaxis in children older than 3 months.	2⊕⊕OO
Recommendation	The guidelines suggest discontinuing antibiotic prophylaxis in children older than 2 years of age if they satisfy all three criteria: (*i*) toilet trained, (*ii*) absence of BBD, and (*iii*) no febrile UTI in the preceding 1 year.	2⊕OOO
Recommendation	Circumcision can be considered as one of the interventions for the prevention of UTI in children at-risk (high-grade VUR or recurrent UTI) of recurrence.	2⊕⊕⊕O
Recommendation	The guidelines suggest cranberry products can be used for the prevention of UTI in children with recurrent UTI and normal urinary tract.	2⊕⊕OO
CPP	All toilet-trained children with UTI should be evaluated for BBD.	Not graded
Recommendation	The guidelines recommend that all children with BBD should be managed with urotherapy for prevention of recurrence of UTI.	1⊕⊕OO
Management of Primary VUR		
Recommendation	The guidelines suggest that surgical reimplantation can be considered in patients with high-grade VUR with recurrent breakthrough febrile UTI on antibiotic prophylaxis.	2⊕⊕⊕O
CPP	In children with high-grade VUR, surgical intervention may be an alternative for parental hesitancy to use antibiotics. When surgical intervention is indicated, patients may be given the option of endoscopic injection of bulking agent as initial therapy with guidance from a physician about its minimally invasive nature but lower success rate as compared to ureteric reimplantation.	Not graded
CPP	Children with high-grade VUR and reflux nephropathy need periodic follow-up to detect long-term complications. Their growth, blood pressure, proteinuria, and kidney function checked during each hospital visit.	Not graded
CPP	Ultrasound is suggested to be performed periodically to monitor the kidney growth in children with persistent high-grade VUR.	Not graded
CPP	The guidelines suggest that DMSA scintigraphy can be repeated during follow-up only in children with recurrence of UTI.	Not graded
CPP	Repeat cystography for documenting resolution of reflux is not required. However, it may be performed after 4-8 years following the initial diagnosis if deemed necessary by treating physicians in children with high-grade VUR.	Not graded
CPP	We suggest screening siblings (aged less than 3 years) of children with primary VUR with an ultrasound scan	Not graded

**GRADE approach was used to determine the strength of recommendation. BBD Bladder bowel dysfunction, CPP Clinical practice point, DMSA Dimercaptosuccinic acid, UTI Urinary tract infection; VUR Vesicoureteric reflux*

especially in infants. Collecting an optimal urine specimen is challenging. In the revised guidelines, we suggest that clean catch should be the preferred method for urine collection except in sick young infants where catheterization or suprapubic aspiration should be used to avoid delay in sending the specimen for urinalysis and culture. Timely initiation of antibiotic therapy is crucial to avoid kidney damage hence rapid screening tests are needed to make a presumptive diagnosis of UTI. While bacteriuria is the best screening test on urinalysis for presumptive diagnosis of UTI, it is cumbersome and not feasible everywhere. The guidelines suggest that a urine dipstick (combination of nitrite and leukocyte esterase) can be used as an alternative to urine microscopy for the presumptive diagnosis of UTI in children. A combination of either nitrite or leukocyte esterase positivity provides better diagnostic accuracy than leukocyturia alone for the presumptive diagnosis of UTI.

Treatment: Initiation of prompt antibiotic therapy

Since delay in initiating antibiotic therapy has been shown to increase the risk of kidney scarring, the guidelines suggest that treatment should be commenced within 48-72 hours of the onset of fever. Third generation cephalos-



[1]Fever (>48 h) without focus in children less than 24 months or with specific urinary symptoms in older children, [2]If feasible to perform urine microscopy (leukocyturia and bacteriuria) can be used as an alternate to the dipstick, [3]Risk factors: bladder-bowel dysfunction, primary vesicoureteric reflux, previous history of UTI, [4]Oral route is preferred over IV except in infants less than 2 months, sepsis and inability to take oral medications, [5]In adolescents where it is feasible to make diagnosis of cystitis, oral antibiotic therapy of 3-7 days is sufficient, [6]MCU study can also be considered in children with UTI due to non-E.coli uropathogens

Fig. 1 Approach to a child with suspected urinary tract infection (UTI)

porins or amoxycillin-clavulanic acid should be used as first-line antibiotics in children with febrile UTI; first- or second-generation cephalosporin can be used for cystitis in adolescents. Oral antibiotic therapy is preferred over intravenous in all children with febrile UTI except in the following settings: (*i*) infants less than 2 months, (*ii*) severely ill children, and (*iii*) those who are unable to tolerate oral medications. The guidelines recommend using a total of 7-10 days of antibiotic therapy for febrile UTI, and a shorter course (3-7 days) for cystitis. Patients not responding to initial empirical antibiotic therapy should be evaluated with an ultrasound scan of kidneys, ureters, and bladder and might require a change of therapy as per the sensitivity of the uropathogens. Patients showing clinical response to initial therapy do not require a change of antibiotic therapy as considerable discrepancy in *in vivo* susceptibility and *in vitro* clinical response has been reported. Response to therapy is chiefly determined based on the resolution of symptoms; urine culture need not be repeated to document response. The guidelines reemphasized that asymptomatic bacteriuria should not be treated with antibiotics.

Imaging: A less aggressive approach for detecting vesicoureteral reflux (VUR) and kidney scarring

Imaging following UTI has traditionally been targeted at detecting underlying anomalies and kidney damage.

Box 1. Definitions

Leukocyturia: Presence of ≥10 leukocytes per mm^3 in a fresh uncentrifuged sample, or > 5 leukocytes per high power field in a centrifuged sample.

Bacteriuria: Presence of one or more bacteria per oil immersion field in a freshly voided uncentrifuged sample.

Acute pyelonephritis: Bacterial infection involving the upper urinary tract (kidney parenchyma).

Cystitis: Bacterial infection localizing to the bladder, characterized by dysuria, frequency, urgency and suprapubic tenderness.

Recurrent urinary tract infection: Two episodes of urinary tract infection during any time period in childhood.

Febrile urinary tract infection: Fever (temperature ≥ 38°C) with positive urine culture defined by the presence of significant colony count of a single uropathogens.

Primary vesicoureteric reflux (VUR): The passage of urine from the bladder back into a ureters and kidneys in the absence of obstructive uropathy and neurogenic bladder dysfunction.

Low-grade vesicoureteric reflux: Grade 1 and 2 vesicoureteric reflux on micturating cystourethrography.

High-grade vesicoureteric reflux: Grade 3 to 5 vesicoureteric reflux on micturating cystourethrography.

Reflux nephropathy: Abnormalities in the renal cortex associated with primary VUR (congenital dysplasia or acquired scarring).

However, none of the existing interventions are effective in reducing the risk of kidney scarring and do not improve long-term outcomes. Hence, the updated guidelines suggest a conservative approach for imaging, primarily aimed at diagnosing high-grade VUR (**Table II**). All children with a UTI should be evaluated with an ultrasound scan of the kidneys, ureters, and bladder. A good quality ultrasound can detect congenital anomalies of the urinary tract or provide a clue for bladder-bowel dysfunction. We suggest performing micturating cystourethrography (MCU) any time after UTI has been treated as per the convenience of patient and physician (generally after 2-3 weeks) in children with recurrent UTI, abnormal ultrasound scan and those younger than 2 years with UTI caused by non-*E. coli* uropathogens. Limiting MCU study to the above indications increases diagnostic yield and avoids unnecessary radiation to many children where the probability of detecting high-grade VUR is low. Acute-phase DMSA scintigraphy has low specificity in detecting high-grade VUR and does not differentiate between permanent kidney scarring and acute pyelonephritis. The guidelines emphasize that acute-phase DMSA scintigraphy should be avoided. The clinician should perform a DMSA scan 4-6 months after an episode of UTI to detect permanent kidney scars. The probability of developing kidney scarring is highest in children with high-grade VUR and recurrent UTI hence we suggest that late phase DMSA scans should be restricted to these categories of patients (**Table II**).

Prevention: Antibiotic prophylaxis is limited to high-grade VUR and for shorter duration

Primary VUR and Bladder and Bowel Dysfunction (BBD) are the two most important risk factors for recurrent UTIs in children [4]. Prevention of febrile UTIs is essential as the risk of kidney scarring increases with the higher number of febrile UTIs [5]. Low dose antibiotic prophylaxis has been considered as a first-line strategy for the prevention of UTI in at risk children. However, recent evidence raised concerns about the efficacy as well as safety of this intervention. The pooled data that included recent studies suggests that antibiotic prophylaxis is not effective in children with normal urinary tract and low-grade VUR. The revised ISPN guidelines recommend giving antibiotic prophylaxis only to children with high-grade (Grade 3-5) VUR (**Table III**). Recent data also suggests that antibiotic prophylaxis is effective in preventing the recurrence of UTI in children with BBD [6]. Considering the importance of BBD in patients with recurrent UTI, we therefore suggest that patients with VUR should be evaluated carefully for the presence of BBD. Patients with BBD should optimally be managed with urotherapy [8] and laxatives to reduce the risk of recurrent UTIs. Urotherapy includes behavioral modifications (regular bladder and bowel habits, adequate fluid intake, optimal posture during voiding etc.) information and demystification related to lower urinary tract symptoms, adequate intervals between urinations, documentations of voiding symptoms and systematic

Table II Imaging following urinary tract infections

Imaging modality	*Indications*	*Advantage*	*Limitations*
Ultrasound scan	All patients	Non-invasive No radiation exposure Provides dynamic images	Operator dependent
Micturating cystourethrography	Patients with abnormal ultrasound scan; Patients aged less than 2 years with non-*E. coli* UTI; Patients with recurrent UTI	Enable grading of VUR Provide detail anatomic delineation of urinary tract	Radiation exposureInvasive; needs catheterization Risk of UTI
Late-phase DMSA scintigraphy	Recurrent UTI	Gold standard for detecting	Radiation exposure Invasive Accessibility

DMSA Dimercaptosuccinic acid; UTI Urinary tract infection; VUR Vesicoureteric reflux

follow-up. We do not advise using antibiotic prophylaxis in children detected to have antenatal hydronephrosis while awaiting evaluation including MCU study. Co-trimoxazole and nitrofurantoin are the two most commonly used antibiotics for prophylaxis in children older than 3 months; cephalexin being preferred for young infants. Clinicians should avoid using broad-spectrum antibiotics such as amoxycillin-clavulanic acid for prophylaxis as this practice increases the risk of antimicrobial resistance. Once initiated, antibiotic prophylaxis may be discontinued in toilet-trained children without BBD and no febrile UTI in the preceding one year. Recent evidence suggests that cranberry products can be used for the prevention of UTI in children with normal urinary tract, however, data for this intervention in children with primary VUR is still limited [7]. Considering multiple and long-term benefits, the guidelines suggest that circumcision may be advised as a potential intervention to reduce the risk of recurrent febrile UTIs in children [8].

Management of Primary VUR: Antibiotic prophylaxis is the first line of management and surgical reimplantation only in patients with recurrent breakthrough febrile UTI.

In patients with primary VUR, neither antibiotic prophylaxis nor surgical reimplantation is effective in reducing the risk of kidney scarring [9], although the latter is more effective in preventing febrile UTIs. The revised guidelines suggest that surgical reimplantation should be reserved for patients with recurrent febrile UTIs despite antibiotic prophylaxis and optimal management of BBD. Endoscopic injection of bulking agents has a lower success rate as compared to surgical reimplantation and hence should be used after careful discussion with the caregivers [9].

Children with primary VUR may have associated kidney damage termed as reflux nephropathy. Kidney damage in these patients is chiefly caused by congenital hypodysplasia but may be also due to kidney scars caused by febrile UTI. Patients with reflux nephropathy may develop proteinuria, hypertension, and rarely impaired kidney function in the long term. Hence these patients require long-term follow-up and monitoring. An ultrasound scan can be used to assess the growth of kidneys. Dimercaptosuccinic acid (DMSA) scan may be repeated in patients with a recurrence of febrile UTI. The median time to resolution is variable depending on the

Table III Strategies for Prevention of Recurrence of UTI in Children

Strategy	*Indications*
Antibiotic prophylaxis	High-grade VUR, recurrent UTI in patients with BBD, Infants with low-grade VUR
Surgical re-implantation	Recurrent febrile UTI despite antibiotic prophylaxis and adequate management of BBD
Cranberry products	Patients with recurrent UTI and normal urinary tract. No data to support its use in patients with VUR
Urotherapy*	All patients with BBD
Circumcision	Can be suggested as an option in patients at-risk of recurrence of UTI

**Urotherapy includes behavioral modifications (regular bladder and bowel habits, adequate fluid intake, optimal posture during voiding etc.) information and demystification related to lower urinary tract symptoms, adequate intervals between urinations, documentations of voiding symptoms and systematic follow-up. BBD Bladder-bowel dysfunction; VUR Vesicoureteral reflux*

grade of VUR therefore if felt necessary, repeat imaging for the resolution of VUR may be done 4 to 8 years after the initial diagnosis. Primary VUR is reported to be common in siblings, however, considering limited intervention to alter the long-term outcome the guidelines suggest that screening should be done using an ultrasound scan only in siblings below 3 years of age. If the ultrasound scan is abnormal or the sibling develops febrile UTI clinicians may consider MCU to confirm the diagnosis of VUR.

CONCLUSION

Timely diagnosis of UTI can be sometimes challenging but is necessary to reduce acute discomfort and long-term consequences. BBD and primary VUR are two important risk factors for recurrence. These updated guidelines present evidence-based systematic and algorithmic guidance for optimal management of these disorders. Updated guidelines lay more emphasis on less aggressive approaches while evaluating, shorter courses of treatment as well as briefer duration of antimicrobial prophylaxis to reduce the burden of antimicrobial resistance.

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PERSPECTIVE

Recent Surge in Mumps Cases in India: Need for Urgent Remedial Measures

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ABSTRACT

Mumps is a global public health problem caused by mumps virus, a member of paramyxoviridae family. MMR (Mumps, Measles, Rubella), an effective vaccine, has been incorporated into routine immunization schedules in over 100 countries. On the contrary, in India, vaccine against mumps has not been included in the routine immunization schedule as mumps is still not viewed as a significant public health problem by the government to warrant such an intervention. An increasing number of mumps outbreaks being reported from many parts of the country in the recent past, is matter of concern. The current paper reviews the situation of mumps in India including the recent surge, and discusses the remedial measures to contain these outbreaks. We conclude that inclusion of Mumps component as MMR vaccine in the Universal Immunization Programme of India along with strengthening surveillance is required to tackle the situation.

Keywords: *MMR Vaccine, Outbreaks, UIP*

INTRODUCTION

India has witnessed a substantial increase in the number of mumps cases, primarily affecting children, in the last few months [1]. This sudden increase in mumps cases has raised concerns among government agencies, healthcare professionals, policymakers, and parents alike. The resurgence of mumps is challenging our healthcare infrastructure and demanding swift, coordinated efforts to curb its spread and mitigate its impact on the vulnerable population, particularly children.

Mumps, an acute highly contagious viral illness caused by a single stranded RNA paramyxovirus, has been a longstanding public health concern, characterized by its sudden onset and association with inflammation of the parotid gland or other salivary glands [2]. Although only one serotype of mumps virus is known, there are 13 genotypes (A to M) that have been determined on the basis of sequencing of the SH protein, which is the most variable protein among mumps strains [3]. Mumps vaccine contains live attenuated strains of virus such as Jeryl-Lynn, RIT 4385, Leningrad-3, Leningrad-Zagreb, Urabe Am9, S79, Rubini, and others, which have been available since the 1960s [4] and most of Indian MMR (Measles, Mumps, Rubella) vaccine manufacturers use the Leningrad-Zagreb strain [5].

Humans are the only known natural host for the mumps virus and the virus spreads through respiratory droplets or direct contact with an infected person's saliva. People with mumps are infectious from 2 days before through 5 days after parotitis onset [6]. Although, natural infection with this virus is thought to confer lifelong protection [2], mumps virus reinfections do seem to occur [7,8]. Complications of mumps occur with or without parotitis or other salivary gland swelling and generally encompass conditions such as orchitis, oophoritis, mastitis, pancreatitis, hearing impairment, meningitis, and encephalitis. Nephritis, myocarditis and other sequelae like paralysis, seizures, cranial nerve palsies, and hydrocephalus have also been reported occasionally. Complications associated with mumps are usually more common among adults than children [2]. Despite its generally low mortality rate, the potential to cause profound morbidity and complications underscores the importance of preventive measures, with vaccination emerging as the most effective solution [9].

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The mumps vaccine, typically administered in combination with measles and rubella as part of the MMR vaccine, has been instrumental in significantly reducing the incidence of the disease since its introduction in 1967 in the United States [10,11]. The success of vaccination programs has been noteworthy, with the incidence of mumps dropping to less than 0.1 case per 100,000 people in many developed countries by 2001 [12]. This achievement demonstrated the effectiveness of wide-spread immunization in controlling the disease, marking a substantial triumph in public health. However, recent years have witnessed a global resurgence of mumps, challenging the assumptions that successful vaccination efforts would lead to the eradication of the disease [13]. Notably, the resurgence has presented an unexpected demographic shift, with a growing proportion of cases affecting vaccinated young adults, contrary to the traditional perception of mumps as a childhood ailment [9,10,13].

The current paper reviews the Indian context of the mumps resurgence, considering factors such as absence of mumps containing vaccine in the routine immunization program, waning immunity among the vaccinated, the impact of new mumps strains, and the challenges of having a robust mumps surveillance system. By comprehensively examining these facets, we aim to contribute to a holistic understanding of the current mumps resurgence, its implications for public health, and the strategies needed to effectively mitigate it.

CURRENT SITUATION OF MUMPS IN INDIA

The Indian context adds another layer of complexity to the global mumps resurgence. As per Global Health Observatory (GHO) data repository, India reported 764 mumps cases between 2021-22, indicating a substantial burden of mumps, particularly affecting children [14]. Previous surges in mumps cases have triggered heightened concerns among government agencies, healthcare professionals, policymakers, and parents alike [15]. The increasing burden of mumps in India underscores the need for a comprehensive understanding of regional variations in disease dynamics, vaccination coverage, and healthcare infrastructure [15].

The rising number of mumps cases among children in Maharashtra, Uttar Pradesh, Odisha and Rajasthan, is a concerning trend [16-18]. The fact that this surge has been observed after a span of 4-5 years raises questions about the factors contributing to the resurgence of the disease in these regions. In October and November 2023, mumps outbreaks in Idukki and Palakad in Kerala, Sivagangai in Tamilnadu, Udupi in Karnataka, and Rajnandgaon in Chhattisgarh, served as poignant reminders of the challenges posed by this infectious disease [16]. The cases primarily emerged among children, presenting with mild fever and swelling. The response to these outbreaks, led by District Rapid Response Teams, involved multifaceted approaches, including community awareness campaigns, house-to-house surveys, and extra immunization sessions [16].

FACTORS CONTRIBUTING TO RESURGENCE OF MUMPS

Several factors may have contributed to this recent rise in mumps cases across India. Despite the recommendations of the World Health Organization [19], the Universal Immunization Programme (UIP) of India does not include mumps vaccine in the routine immunization. In India, children are offered the MR vaccine in a two-dose strategy for children at 9 and 15 months to cover measles and rubella but not mumps [20]. MMR vaccine is only available in the private sector in India and remains out of bounds for over 80% of the children of the country [21].

One of the important reasons for mumps resurgence in India, which has predominantly a naive child population due to the absence of mumps component in UIP, is because prior to introduction of vaccination, mumps was an epidemic disease, with a cycle of 4-5 years [22]. A meta-analysis performed to assess immunogenicity and waning rate estimates for the measles, mumps, and rubella components of MMR vaccines concluded that there is significant annual waning of immunity for mumps component among the vaccinated individuals [23]. An important reason for waning of immunity, among the vaccinated ones, might be ascribed to the alterations between the circulating and vaccine strains [24]. Additionally, overcrowding, inadequate sanitation, and limited and remote access to healthcare facilities in certain regions may facilitate the rapid spread of the virus [25].

REMEDIAL MEASURES

Inclusion of MMR over MR Vaccine in Universal Immunization Program

The inclusion of the MMR (Measles, Mumps, Rubella) vaccine in the universal immunization Program (UIP), in place of MR (Measles, Rubella) vaccine, emerges as a potential remedial measure which is also based on comprehensive studies on mumps-containing vaccines in India. Longitudinal follow-up studies of the indigenously produced MMR vaccine demonstrated excellent immunogenicity and low reactogenicity of the mumps component and high sero-positivity for mumps-specific antibodies even after 6 years of vaccination, emphasizing its effectiveness [26,27]. However, the need for two doses of the vaccine is highlighted to boost circulating antibodies adequately [27,28]. Adding the third dose of MMR was

found to be effective in outbreak settings among children who had a longer period since vaccination [29].

While challenges, such as limited seropositivity in some studies, underscore the importance of large-scale investigations [30], the overall evidence supports the inclusion of the MMR vaccine in India's UIP to mitigate the burden of mumps and associated complications [13,15,21]. WHO as well as the Indian Academy of Pediatrics (IAP) recognize the MMR vaccine as a highly effective way of preventing mumps and the IAP includes it in its vaccination schedule for children and adolescents [31].

Healthcare Infrastructure Strengthening and Environmental Modifications

The recent mumps outbreaks in various parts of India also emphasize the value of a robust healthcare infrastructure capable of promptly identifying, segregating, treating, and containing infectious diseases. Improving diagnostics, ensuring an adequate supply of medicines and vaccines, and training healthcare professionals to recognize and manage mumps cases are essential steps in mitigating the impact of the outbreak. Environmental modifications compatible with a healthy lifestyle may further help in disease mitigation [32]. Addressing the social determinants such as overcrowding, poor sanitation and hygiene is essential to create an environment less conducive to the transmission of mumps and other infectious diseases.

Strengthening Mumps Surveillance System

Investing in surveillance systems can provide timely data to guide public health interventions to contain re-emerging infectious diseases like mumps [33]. The mumps surveillance in India is mainly done through Integrated Disease Surveillance Programme (IDSP), an infectious disease surveillance system under National Centre for Disease Control, Ministry of Health and family Welfare, Government of India. [34]. However, IDSP only records outbreaks of mumps currently and mumps is not included in the list of notifiable diseases. IDSP worked actively during the outbreaks of mumps in Kashmir in 2017 [35]. WHO's vaccine preventable diseases (VPD) surveillance system in India also does not include mumps as mumps containing vaccine is still not part of UIP. Another surveillance system for mumps existing in the country is "IDsurv", an IAP initiative which is an Infectious Disease Surveillance and AEFI (Adverse Event Following Immunization) reporting system. The surveillance system mainly relies on reporting by the private practitioners [36]. Overall, mumps surveillance in India is not of satisfactory standards and requires an integrated approach both from government and private sectors. For improving the mumps surveillance, IDSP should include the disease in the list of routinely reported diseases. As per WHO, surveillance for mumps need to be tailored according to the level of control to match specific objectives which monitor disease burden and trends over time, identify and respond to outbreaks and find populations requiring additional disease control measures for mumps [37]. For the same, it recommends 6 indicators for assessing the performance of mumps surveillance: *i*) completeness and *ii*) timeliness of reporting, *iii*) timeliness of investigation, *iv*) adequacy of specimen collection, *v*) timeliness of specimen transport and *vi*) timeliness of reporting laboratory results and the target level for a good surveillance system is ≥ 80% for each of these indicators [37]. WHO's VPD surveillance should include mumps in India for the same which currently only include measles and rubella. Further, mumps surveillance in the country could only be made as robust as AFP and measles surveillance through the combined effort of IDSP, NCDC and WHO. IAP could play a major role in improving the mumps surveillance through increased reporting of mumps cases through the network of pediatricians working in govt and private sectors and training the medical officers on mumps case identification and management. Further, regular monitoring of the surveillance indicators needs to be undertaken to identify areas of weakness and specific areas of the surveillance system that require corrective actions.

Public Awareness and Education

A critical component of controlling the mumps outbreak lies in public awareness and health education [38]. All parents may not be fully informed about the route of transmission of mumps and importance of vaccinations. Myths should be removed through targeted health education.

Global Collaboration and Lessons from Other Countries

India can benefit from international collaborations and learn from the experiences of other countries that have successfully controlled mumps outbreaks [39]. In Israel, for example, a comprehensive ring vaccination campaign was performed to contain the spread of mumps during outbreaks in the Israeli civilian and military populations [40]. Sharing best practices, research findings, and strategies for vaccine delivery can contribute to a more effective response. Collaboration with international health organizations can also facilitate the procurement of vaccines and necessary resources to address the outbreak comprehensively.

CONCLUSION

The recent outbreaks of mumps reported from different

parts of in India serves as a harsh reminder for the inclusion of mumps vaccine in UIP along with strengthening the surveillance system and building resilient healthcare system. As the nation struggles with this public health challenge, a multifaceted approach involving public awareness campaigns, healthcare infrastructure strengthening, government intervention, and global collaboration is essential. It is imperative for all stakeholders, including government agencies, healthcare professionals, policymakers, parents, and the global community to come together to ascertain the root cause of these outbreaks to implement a sustainable solution. Through collective efforts, India can not only contain the current surge in mumps cases but also build a foundation for a more resilient and responsive healthcare system to protect the wellbeing of its children.

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Protecting Child Health From Air Pollution in India

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ABSTRACT

Recent research has underscored the diverse ways in which air pollution detrimentally affects child health in India. Notably, India shoulders one of the highest burdens of mortality of children under five years of age globally due to exposure to air pollution. Distinct mitigation strategies are vital to reduce air pollution exposure and its resultant health burdens among children in India when compared to strategies applicable in the global West. This necessity arises due to the substantial influence of residential combustion of solid fuels, and considerable disparities prevalent among India's population. Addressing these unique challenges requires widespread awareness, community engagement, and sustainable policies. As India embarked on a mission to reduce air pollution, showcasing health benefits linked to interventions is crucial. Augmenting access to health data is equally essential to bolster evidence-based policymaking aimed at reducing the child health burden stemming from air pollution in India.

Keywords: *Ambient and household exposure,Child mortality, Environment, $PM_{2.5}$, Health burden*

INTRODUCTION

Exposure to criteria pollutants such as fine particulate matter less than 2.5 µm in diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) results in various health issues, encompassing morbidity and mortality related to cardiovascular diseases, respiratory diseases, and many other ailments [1,2]. Children under five years of age (U5) are among the most vulnerable groups being impacted by exposure to air pollution due to their developing bodies and immature immune systems [3,4]. In India, the longstanding challenge of poor air quality has had alarming impacts on the health of children [3,5,6]. Despite the implementation of multiple policies intended to mitigate air pollutant emissions, the country grapples with persistently high levels of air pollution. Over the past two decades, i.e., between 2000 and 2018, the population-weighted exposure to ambient $PM_{2.5}$ in India has risen significantly, after which it seems to show a sign of stabilization [7]. This pattern sharply contrasts with the global pattern of improving air quality [8]. Concurrently, NO_2 exposure within India surged by 17% during this timeframe, in contrast to the 10% global decrease. These decreasing global trends are largely attributed to successful policy implementations in the global West and East Asia, contributing to improvements in global air quality [9].

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Where does India stand globally in terms of child health burden attributable to air pollution?

The Global Burden of Disease (GBD) study [2,10], examining the impact of diseases, injuries, and risk factors worldwide, indicates a significant decline in deaths among U5 children due to exposure to $PM_{2.5}$ in India. This rate reduced notably from 418 deaths per 100,000 population in 1990 to 127 deaths per 100,000 population in 2019, primarily driven by a decrease in household air pollution. A recent study revealed that over 11% of worldwide deaths resulting from ambient $PM_{2.5}$ occur among children U5 in India [11]. **Fig. 1*a*** depicts the deaths among children from exposure to ambient $PM_{2.5}$ with data from Chowdhury et al [11]. Comparatively, in the global West and East Asia, this percentage is less than 1%. In African nations like Nigeria and the Democratic Republic of Congo, this percentage rises to over 40% (**Fig. 1*b***). In addition to high ambient $PM_{2.5}$ exposure, due to its sizable population of U5 children (17% of the global total), India contributes to 34% of all deaths in this age group caused by exposure to ambient $PM_{2.5}$.

Though exposure to NO_2 is not included in the current GBD assessments, studies have associated NO_2 exposure with incidences of asthma among children and adolescents [12]. In 2015, exposure to NO_2 was associated with 0.3 million (95% confidence interval 0.17-0.52) cases of asthma among children and adolescents in India. This accounts for 20% of all asthma cases within this age group in the country. Compared to the numbers estimated in

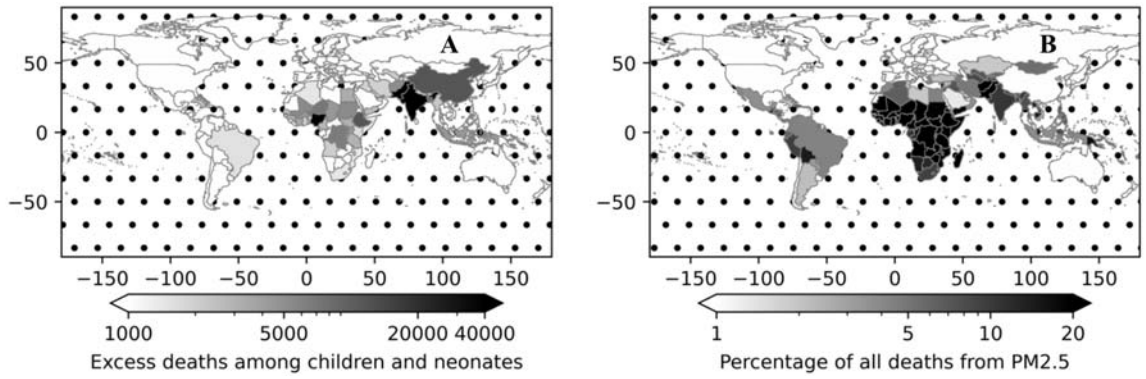

Fig. 1. (*a*) Excess deaths from exposure to ambient $PM_{2.5}$ among U5 children (including neonates). (*b*) Excess deaths among U5 children are expressed as a percentage of all deaths from exposure to ambient $PM_{2.5}$.

India, the incidence of asthma related to NO_2 exposure in Western Europe and the United States was nearly 3 times and 1.5 times lower, respectively.

While the GBD study provides a comprehensive framework for understanding the impact of air pollution on human health, studies in developing countries like India are quite limited. Earlier research lacked robust geospatial data for epidemiological analysis and instead used spatiotemporally coarse pollution measures relying on a handful of ground monitors. These exposure estimates are plagued by the disadvantages of errors and exposure misclassification. As satellite-derived $PM_{2.5}$ prediction models [e.g., 7] have evolved, there has been a gradual shift towards utilizing spatiotemporally resolved ambient exposures. Recently, numerous studies (**Fig. 2**) have established associations between satellite-derived ambient $PM_{2.5}$ data and geo-coded child health data from the National Family Health Survey (NFHS). Simultaneously, studies also explored the association of child health outcomes with household air pollution, thereby producing evidence on child health outcomes such as anemia [5,13,14], stunting [13,15], low birth weight [5,16,17], acute respiratory infection [3,5,18], and even mortality [19-21].

Addressing child health burden attributable to air pollution in India - How is it different?

Children's health in India requires unique attention compared to other regions due to several distinctive factors.

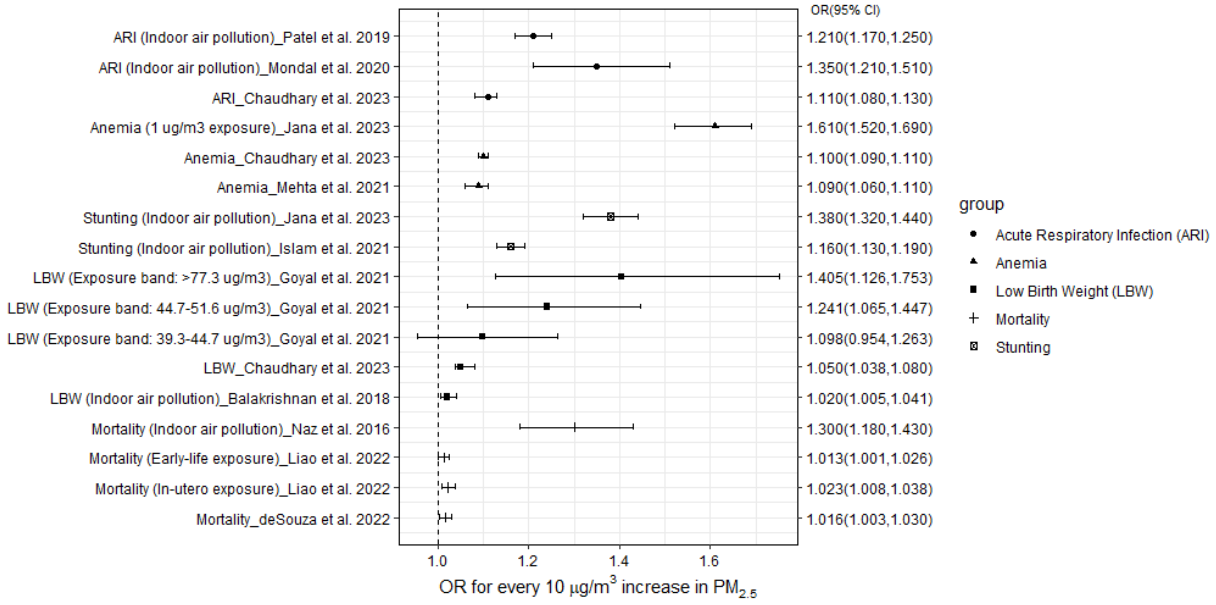

Fig. 2 Forest plot showing the studies that assessed the association between $PM_{2.5}$ exposure and a range of health outcomes among U5 children

Household air pollution is a big problem

All the studies attempted to understand the sectoral contributions to ambient air pollution in India unanimously point towards indoor combustion of solid fuels for cooking, heating, and various household activities as the leading cause of excess deaths associated with ambient $PM_{2.5}$ among U5 children in India [22,23]. These studies indicate a variable range of contributions, from 20 to 50% of total deaths in this age group. Furthermore, this indoor exposure to air pollution adds to the toll, accounting for an estimated 68 (45-96) thousand deaths [2,10]. These figures starkly outweigh the contributions from more common urban sources like transportation, industries, and power generation, which play a dominant role in causing excess deaths related to ambient $PM_{2.5}$ in the global West and East Asia [11]. Likewise, concerning exposure to NO_2, while transportation is the largest contributor to NO_2-related asthma incidences globally, contributing to up to 70% of asthma incidences in North America and Western Europe; the leading source in India is the use of solid fuels within households [12]. These findings underscore the increased significance of social programs such as the Pradhan Mantri Ujjwala Yojana (PMUY) in India.

Social inequality is a major concern

Economic inequalities notably impact children's vulnerability to air pollution and its health effects, particularly in India. Recent studies highlight that families in rural areas and those facing poverty in India have elevated exposure to $PM_{2.5}$, raising the risk of respiratory illnesses in U5 children from disadvantaged socioeconomic backgrounds [24]. Moreover, households with limited resources rely on cheap and easily accessible polluting fuels for cooking and other household activities leading to enhanced indoor air pollution exposure. Children in economically disadvantaged communities encounter difficulties in accessing quality education, which could otherwise raise their awareness about air pollution. In India, over 60% of the child population resides in rural areas, yet the National Clean Air Program (NCAP) primarily focuses on reducing air pollution in selected cities, thus overlooking the significant rural population. An airshed-based approach to encountering major sources of air pollution by region is of utmost importance. Bridging these gaps requires comprehensive approaches that prioritize access to clean energy, healthcare, and education, aiming for equal opportunities for all children regardless of their location or socioeconomic status. Additionally, there is an urgent need for increased data availability to drive comparative research addressing environmental justice concerns.

Lack of India-specific studies on air pollution and health impacts

Health impact assessments are based on exposure-response curves that are developed using data from developed countries, and most importantly, they assume uniform toxicity for all $PM_{2.5}$ species. The counterfactual exposure levels are too low and most likely unattainable for India, given the high background dust [11]. Developing India-specific exposure-response functions and under-standing their sensitivity to sectoral $PM_{2.5}$ is important. For many health outcomes, $PM_{2.5}$ has been considered as the exposure metric. Moreover, health outcomes are the manifestation of exposure to multiple air pollutants (not just $PM_{2.5}$) and their toxicity levels. Chaudhary et al. [5] conducted the sole Indian study assessing the differential effects of $PM_{2.5}$ species on children's health.

There is a need for additional studies of a similar nature, particularly in a cohort setting, which will help in tracing the target emission sector contributing to exposure. Given the increased susceptibility of children to air pollution compared to adults, there is an urgent need to align environmental policies with the national health mission. To advance research on air pollution epidemiology in India, access to health data is crucial.

What are the consequences?

The health hazards among U5 children posed due to in-utero and early-life exposure to air pollution were earlier summarized by Dey [25]. Studies have established that $PM_{2.5}$ can permeate the placental barrier during in-utero exposure, leading to oxidative stress and subsequent changes in the placenta [26]. Oxidative stress and placental inflammation may disrupt the transplacental exchange of nutrients and oxygen, thereby affecting fetal growth. Low birth weight increases the risk of malnutrition [27]. The early life exposure to $PM_{2.5}$ results in compro-mised immunity via oxidative stress and inflammation. Delays in physical development in early childhood can have serious negative long-term consequences for adult life [28]. Air pollution exposure can adversely affect the child's learning outcomes [29], thereby impacting the child's future.

India's National Health Policy (NHP) 2017 has set a target of reducing U5 mortality below 23 deaths per 1000 live births and neonatal mortality below 16 deaths per 1000 live births by 2025. Malnutrition and air pollution are the first and third most important risk factors for child mortality in India [30]. Mitigating air pollution will, therefore, directly and indirectly (by reducing the prevalence of malnutritional outcomes) accelerate India's

progress towards meeting the NHP target.

What should be done?

Despite significant strides made in India's endeavors to decrease U5 child mortality rates through focused interventions and healthcare programs emphasizing maternal and child healthcare services nationwide, the considerable threat stemming from exposure to air pollution tends to be overlooked. These impacts on children are expected to be compounded by global climate change, highlighting the urgent need for policymakers to promptly prioritize and address the mitigation of primary and secondary sources of air pollution.

Minimize exposure in children's primary micro-environments

Efforts aimed at reducing emissions should concentrate on microenvironments where children primarily spend their time, such as homes and schools. Air pollution levels within school premises are notably affected by their proximity to roads and nearby industrial or power plants and are influenced by the presence of green spaces in the vicinity. Research indicates that implementing measures like traffic restrictions, establishing 'school streets' (with traffic bans during school entry and exit times in the immediate school vicinity), or relocating drop-off/pick-up points away from school entrances have the potential to decrease exposure to air pollution in and around schools [31].

Access to clean energy can significantly reduce household $PM_{2.5}$ exposure [32]. The PMUY has effectively disbursed over 90 million Liquefied Petroleum Gas (LPG) connections nationwide, yet ensuring the continued adoption of clean fuels through a sustainable financial model poses an ongoing challenge [33]. However, for accelerated progress, stricter implementation of clean air action plans and technological innovations are the way forward.

Include evidence on children's health in air quality policies

Policy makers and regulatory bodies traditionally do not take impacts on children fully into account while developing guidelines and thresholds for air pollution exposure. Implementing stricter air quality standards aimed specifically at safeguarding children's health in India is crucial in ensuring a healthier environment for their growth and reducing the prevalence of acute and chronic diseases linked to air pollution exposure.

Effective communication and awareness

There is a lack of widespread awareness regarding air pollution that persists in regions beyond major cities in India, particularly in the entire Indo-Gangetic plain, encompassing rural areas. Despite $PM_{2.5}$ levels surpassing national standards, there is a lack of awareness among citizens regarding the adverse effects of air pollution, particularly on children. Physicians could serve as advocates for promoting clean air practices, but many of them lack awareness of the diverse health risks associated with air pollution extending beyond respiratory issues. More effective communication is required to drive behavioral changes at individual and community levels that can accelerate the implementation of policy and technological interventions initiated by the central and state governments.

Access to air pollution and health data

For the rapid progression of air pollution epidemiology research in India, focused capacity-building programs promoting interdisciplinary skills is imperative. In recent years, CAPHER-India (*capherindia.org*) and GeoHealth India (*https://www.ceh.org.in/activities/geohealth/*) networks were created to cater to the skill development needs in air pollution epidemiology. The accessibility to health data also plays a pivotal role in conducting comprehensive studies focusing on air pollution health effects and aids evidence-based policymaking. Health needs to be made an integral part of the NCAP with a broader and enhanced scope to address ambient and household air pollution seamlessly, cutting across the urban-rural transact to protect children from the peril of air pollution.

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UPDATE

The Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers Version 6

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INTRODUCTION

Decades of advances in the diagnosis and treatment of childhood cancer have improved the survival of children with cancer, with a 5-year overall survival of > 80% in high-resource settings and a consequent increase in survivors [1]. Survivors of childhood, adolescent and young adult (CAYA) cancer are at risk of chronic health conditions, organ dysfunction, mental and reproductive health issues, subsequent neoplasms as well as long-term financial and psychosocial issues [1,2]. Late effects are defined as therapy-related complications or adverse effects that persist or arise after completion of therapy, and are generally related to the effects of cancer treatment, the cancer itself or sometimes due to host factors [1]. Survivors of childhood cancer at high risk of late effects need systematic, risk-adapted, specialized and focused care for early diagnosis and anticipatory management of these sequelae [1,2].

Children's Oncology Group Long Term Follow-up Guidelines

Several collaborative groups have formulated guidelines and recommendations for long-term follow-up of survivors of CAYA cancers, notably the Children's Oncology Group Long-Term Follow-Up Guidelines (COG LTFU), the Pan-European Network for Care of Survivors (PanCare) recommendations and the International Guideline Harmonization Group for Late Effects of Childhood Cancer (IGHG) guidelines [3-5].The first to be developed, the COG LTFU guidelines represent a collaborative effort between the Nursing Discipline and the Late Effects Committee of the COG [3]. Starting with the first version in 2003, these guidelines have been updated at least every 5 years, and the most recent version (version 6) was released in October 2023. Similar to the previous versions, the most recent version of the COG LTFU guidelines focus on those who have completed cancer therapy for two or more years. The guidelines are risk-based, exposure-related clinical practice guidelines for screening and management of late effects. The current guidelines are based on 165 therapeutic exposures that describe the specific chemotherapy agents and their doses, and the sites and doses of radiotherapy possibly received by the individual.

There are also recommendations for periodic evaluation and suggestions for health counselling. These guidelines can help early identification of late effects and appropriate intervention, thus reducing or ameliorating the burden of morbidity. The accompanying website also contains a Program Resource Guide and health link appendices (materials for clinical application and health links) which are of great practical value [3].

Need for Revision

The initial guidelines in 2003 were graded using the modified version of the process established by the National Comprehensive Cancer Network, integrating available literature with expert opinion. Subsequently, creation of multidisciplinary task forces which monitor medical literature have provided periodic reports to the COG Outcomes and Survivorship Committee, and have recommended revisions, leading to periodic updates. A fast-expanding body of evidence, much of which comes from several well-conducted studies on large populations of childhood cancer survivors, have demonstrated associations between specific exposures and late effects necessitates regular updates including the most recent one. For instance, evidence regarding the doxorubicin-

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equivalent doses of daunorubicin and mitoxantrone was recently amended based on evidence from a large cohort of survivors [6]. The guidelines have also been modified to include recommendations from the IGHG guidelines including the risk stratification for cardiomyopathy.

Important Changes in Version 6

Due to the large number of therapeutic exposures and potential late effects in children with cancer, the guidelines have been lengthy and complex out of necessity. However, not all children go on to develop late effects, especially those treated in recent years. The current version has attempted to simplify these guidelines in multiple ways (**Table I**). An analysis of the COG LTFU guidelines showed that only certain tests had a high-yield (e.g. thyroid function, audiometry, dual-energy x-ray absorptiometry scans and pulmonary function testing), suggesting that testing should be targeted and evidence-based [7]. The current COG LTFU guidelines thus lay emphasis on the use of history and physical examination which, in turn, direct screening tests (**Table II**).

The incorporation of targeted/biological/ immune-directed therapies into the frontline treatment of children with cancer has raised concerns about the potential late toxicities [1]. With the available evidence, recommendations have been made only for long-term surveillance post Tyrosine Kinase Inhibitors (**Table II**) and future versions will build on this as more information becomes available.

Implications for Clinical Practice

Survivorship care is nascent in India and other low- and middle-income countries (LMICs), and structured long-term follow-up may not exist at most centres [8]. The COG LTFU guidelines are followed at several centres in India and are feasible and helpful in our personal opinion [9]. However, the data on late effects from India and other LMICs suggests that the profile of late effects as well as priorities for survivorship care may differ from that in Europe and North America, leading to efforts to develop adapted long-term follow-up guidelines [8-10]. The healthcare policies and systems (including lack of insurance in cancer survivors) in countries like India are not conducive to delivery of care to cancer survivors [8-10]. There is poor access to cancer screening recommendations for asymptomatic adult survivors of CAYA cancer since robust mechanisms of transition to adult services (primary, secondary or tertiary) do not exist. Oncofertility is still limited to certain centres [8].

In this context, the emphasis on history and physical examination followed by limited screening evaluation is a welcome change, not only in limited-resource settings but also to reduce time, effort and cost to the survivor and family. Additionally, detailed treatment data, especially radiation dosimetry and exact fields is not available to the clinician in our setting. The current version of the COG LTFU provides recommendations for surveillance without the need for intricate details of treatment.

Many survivors treated in recent decades may have only mild late toxicities, and the focus in them would be health promotion. The exhaustive list of health links within the COG LTFU guidelines is especially useful in this context. Complementing the COG LTFU guideline is a web-based interface, known as "Passport for Care," that generates individualized exposure-based recommendations from these guidelines in a clinician-focused format

Table I General Changes

Changes	*Details*
Simplification of guidelines / 'user-friendly'	Focus on clinically relevant content
	Use of hyperlinks to facilitate navigation especially to health links
	Finer details of treatment especially radiation fields and exact doses are now not required for surveillance recommendations
	Addition of cyclophosphamide equivalent dose (CED) calculator
General	Increased focus on clinical exam and history
	International Guideline Harmonization Group screening recommendations have been incorporated
Updated terminology	Secondary malignancy is now 'Subsequent malignancy'
	Reduced ovarian follicular pool is now 'Diminished ovarian reserve (DOR)'
	Veno-occlusive disease (VOD) is now 'Sinusoidal obstruction syndrome (SOS)'
Significant new sections/late effects added	Subsequent malignancy and/or Risk of malignancy in offspring of survivors
	Targeted/biological or immunological therapies

Table II Changes in Screening Recommendations

Changes	*Details*
Guidelines for genetic risk assessment for predisposition to cancer	Survivors with genetic predisposition need surveillance for subsequent malignancy; for for offspring may need surveillance based on genetic risk factors
Cardiomyopathy screening	No longer recommended for individuals with either < 15Gy radiation to heart or cumulative doxorubicin-equivalent anthracycline dose <100 mg/m^2; Mitoxantrone cumulative dose now to be multiplied by a factor of x 10 (previously x 4) for the doxorubicin-equivalent anthracycline dose.
Screening for subsequent malignancy	Screening guidelines are presented only for those at high risk of developing subsequent malignancies based on the history of therapeutic exposures
	cancer screening for average risk (non-high risk) individuals to be done as per physician discretion
	Monthly breast "self-exam" is no longer recommended
Testicular hormonal dysfunction related to alkylating agents and/or testicular radiation	Recommend screening in high-risk patients starting at age 18 years (AM testosterone)
Reduced bone mineral density (BMD) related to steroids and HCT	Guidelines are presented in an algorithm. Vitamin D recommendations updated as per updated American Academy of Pediatrics (AAP) guidelines
Cataracts related to corticosteroids, alkylating agents, and/or radiation	Yearly evaluation by an ophthalmologist
Novel agents	Growth problems and hypothyroidism may be related to BCR-ABL tyrosine kinase inhibitors
	Immunologic complications may be related to B-cell directed antibody-based therapies
	Other targeted /biological therapies: insufficient information to make recommendations
Late effects association removed for certain exposures	Methotrexate is now not considered to have known renal or BMD late effects High-dose cytarabine is now not considered to cause clinical leukoencephalopathy

for ease of patient-specific application of the guidelines in the clinical setting. Creation of a similar platform in India can be very valuable to parents, survivors and clinicians and is an area of priority.

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Tuberculosis Therapy in Children: Past, Present and Future Perspectives

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INTRODUCTION

Tuberculosis (TB) accounts for the greatest global mortality attributable to a single infectious disease, barring SARS-CoV2 [1]. Among children, the annual world-wide burden of TB is estimated to be 12 lakh cases, representing about 1 in 8 of the total cases, but contributing to 1 in 6 deaths. In our country, the Indian Academy of Pediatrics has been at the forefront of advocacy and education in childhood tuberculosis. This issue of *Indian Pediatrics* marks the 50th year of publication of an important research paper exploring the optimal treatment of childhood TB [2].

THE PAST

Although TB has 'plagued' humankind for millennia, Koch's discovery of the etiology paved the way for its rational therapy. As recently as the mid-20th century, clean air and bed rest (provided by admitting patients to sanatoria) were the mainstays of management. However, an Indian trial evaluating sanatorium versus home-based management, found comparable results [3], setting the stage for shutting down TB sanatoria. For decades, therapeutic approaches in TB included creating pneumothorax, lung resection, artificial pneumoperitoneum, thoracoplasty, and phrenic nerve crushing [4]. The near simultaneous discovery of the clinical benefit of two antimicrobials – para-aminosalicylic acid (PAS) and streptomycin - launched the era of tuberculosis chemotherapy [5,6]. Within a few years, isoniazid was identified as a more efficacious, safer, and better tolerated medication., leading to 'triple therapy' with all three agents. During the early 1960s, ethambutol was discovered and found to have equivalent efficacy to PAS. By the latter part of the same decade, rifampicin was identified as a potent anti-tuberculosis agent; com-bining it with isoniazid and ethambutol, reduced the treatment duration to nine months [7]. Despite the exciting break-throughs during 1950-1970, childhood TB was generally ignored. It is against this backdrop that the paper published by Dingley and Sehgal [2] gains signi-ficance.

The study [2] randomly allocated (please note the difference from the term 'randomized') 280 hospitalized children (<14y) having pulmonary tuberculosis, to receive 6 months therapy with isoniazid, in combination with either ethambutol, PAS, streptomycin, or thiacetazone. About one-fourth of the enrolled children dropped out during the first month of therapy, and 209 completed the trial. The authors provided reasons for the drop-out/exclusion which were distributed fairly uniformly across the four treatment regimens.

Although the basis for diagnosing TB was not specified, every child had radiographic features suggesting TB. This included parenchymal lesions in 60% (including cavity in 80% of these) or non-parenchymal lesions in 40% (mediastinal nodes, primary complex, pleural effusion) and primary complex. Almost two-thirds had microbiologically confirmed TB demonstrated by sputum smear positivity. These were presumably also culture-positive as pre-therapy antimicrobial susceptibility was also reported. The baseline radiological and microbiological characteristics appeared similar in the four trial arms.

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The main outcomes were microbiologic negativity, and radiographic resolution. For this, the authors meticulously performed sputum examination and antimicrobial susceptibility (every month), and chest radiography (at 3 and 6 months). Blood tests for liver toxicity and eye examination (for ethambutol toxicity) were also performed. To cut a long story short, the investigators identified comparable microbiologic conversion, and radiographic resolution/improvement amongst the four therapy groups. A few children developed undesirable effects, but none required cessation or switch of therapy. Interestingly, there were no adverse events in those receiving ethambutol. The authors concluded that the combination of isoniazid with ethambutol was superior to the other combinations [2].

It is remarkable that this 50-year-old trial included multiple research refinements such as random allocation of participants, microbiological plus radiologically diagnosed TB, intensive microbiologic analysis during therapy, multiple objective outcome parameters, and meticulous reporting. This provides a wealth of data for multiple analyses. Although the lack of clinical data and a few methodological issues may reduce some confidence in the results, on-the-whole, the trial is illustrative as well as instructive for present-day researchers.

THE PRESENT

Until very recently, childhood TB was not accorded great importance by public health specialists, global bodies, national agencies, and funding organizations; believing that it contributes minimally to the global burden. This may partly explain why even the age limit for pediatric TB is generally considered as 15y, unlike 18y for almost everything else. Therefore, therapy was mostly extrapolated from strategies designed for adults. Pulmonary and most extrapulmonary TB is therefore treated with a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol for two months; followed by rifampicin and isoniazid for another four months [8]. India recently added ethambutol in the continuation phase as well [9]. Pediatric drug dosages are also extrapolated from pharmacokinetic data of adult patients. Even the intermittent administration of medications under the "Directly Observed Therapy Short course" (DOTS) and DOTS Plus initiatives were implemented in children to align with the strategy for adults. Although the intermittent administration of medications under the DOTS strategy was wholeheartedly endorsed [10] and the strategy itself declared 'successful', later data suggested that the intermittent regimen was associated with a trend towards inferior cure rates [8], necessitating a reversion to daily therapy.

Thankfully, the current decade witnessed a greater focus on childhood TB, with better diagnostic tools, pediatric preparations of many anti-TB medications, shortened treatment duration, as well as simplified classification and treatment regimens. Part of this focus went hand-in-hand with enhanced funding for childhood TB, which finally reached levels proportionate to the disease burden in 2020 [11].

These initiatives led to the upward revision of the dosages for the first-line antimicrobials based on pediatric pharmacokinetics (current doses include isoniazid 10-15 mg/kg instead of 5 mg/kg, rifampicin 10-20 mg/kg instead of 8-12, pyrazinamide 30-40 mg/kg, and ethambutol 15-25 mg/kg) [12]. Other noteworthy progress included clinical trials of modified treatment regimens (duration and drugs), pediatric trials on delamanid, bedaquiline, and levofloxacin, US FDA approval for rifapentine in children older than 2y, and the development (as well as approval) of pediatric preparations of multiple drugs including isoniazid, pyrazinamide, ethambutol, moxifloxacin, cycloserine, delaminid, and clofazimine [11].

In India too, the official TB program laid emphasis on pediatric TB, aligning it with the Revised National Tuberculosis Control Programme [10,13]. The initial three-level categorization of disease [10] (with their diverse treatment plans and durations), has been recently replaced with a common treatment regimen for almost all categories of tuberculosis (including newly diagnosed TB, whether pulmonary or extra-pulmonary, clinically labelled or microbiologically confirmed, and also those previously treated) [14].

The current World Health Organization (WHO) guideline for pediatric TB recommends reducing the treatment duration in children with "drug susceptible, non-severe TB" to four months [15]. Non-severe TB was defined by the criteria in the single trial on which the recommendation was based [16], viz. lymph node (peripheral or mediastinal) TB, uncomplicated pleural effusion, and "paucibacillary, non-cavitary, non-miliary pulmonary TB confined to one lobe". The WHO guideline also permitted reducing the treatment duration in tubercular meningitis, to 6 months, but with 4 drugs (isoniazid, rifampicin, pyrazinamide, and ethionamide) administered throughout the course [15] (as practised in South Africa for almost ten years) [17]. The WHO guideline has been critically appraised [18], highlighting the inadequate scientific justification for shortening the regimens, and inappropriateness for the Indian setting. However, although the basis for the recommendation is questionable, well-designed trials are likely to report similar findings viz. that shorter durations are efficacious for non-severe forms of childhood TB. The key question is whether shorter regimens would work in all forms of intrathoracic TB,

thereby obviating the need for clinicians to prescribe cumbersome and expensive investigations to identify those conforming to the criteria in the guideline [15,18].

Among the nearly 12 lakh pediatric TB cases, about 25-30 thousand are rifampicin resistant [19,20]. Therapy of drug resistant TB in children faces the twin challenges of long duration, and intolerance to medications (due to prolonged injections, unpleasant taste, etc.). The former has been successfully addressed by recommending shorter, all-oral regimens even in children [21,22], although this is not based on pediatric trials. The latter is being tackled by the development of child-friendly preparations that are not only more palatable, but allow more accurate dosing [23].

Despite these laudable advancements in the treatment of childhood TB, some gaps remain. These include identifying the optimal biological specimen for TB diagnosis in infants and children (at the point of care), implementing cost-effective and efficient diagnostic tools for microbiologic confirmation, robust definitions for 'clinically diagnosed TB', evaluating the optimal strategy to manage latent tuberculosis, preventing transmission to and from children, prophylaxis against drug resistant TB, and optimal management of TB HIV coinfection.

THE FUTURE

Unlike the situation over 50 years back, there is very low likelihood of discovering new drugs effective against TB. In fact, potentially new pharmacotherapies are currently broadly classified as *i*) newer medications (bedaquiline, delamanind, pretomanid), *ii*) repurposed medications (clofazimine, linezolid), and *iii*) newer applications of available medications [24].

Emerging data suggest that rifampicin administered in higher doses than conventionally used, may have greater efficacy. Studies in adults suggest that daily doses as high as 40-45 mg/kg are not only more efficacious, but also safe and well-tolerated [24]. A study in children recorded the safety of 60 mg/kg rifampicin, albeit for two weeks only [25]. The Operational Handbook [26] released with the latest WHO pediatric TB guidelines [15] also advocated rifampicin doses of 22-30 mg/kg for tubercular meningitis.

Similarly, rifapentine (which has greater potency and duration of action) may be an option, although it is only recently being considered for infants younger than 2y old. A shorter four-month regimen with rifapentine and moxifloxacin (4 drugs for 2 months, followed by 3 drugs for the next 2 months) has already been permitted in the latest WHO guideline [15]. Thus, it is probable that the future will witness more effective and/or efficient ways of using the existing medications.

It is also interesting that the quest to shorten and simplify TB treatment regimens 50 years back, continues even today. The results of some recent pediatric trials exploring alternate and shorter TB regimens in childhood TB (including TB meningitis) suggest that alternate regimens, shorter regimens, and combination of both strategies, could be efficacious, but the enhanced efficacy needs to be balanced against safety.

Genetic and/or metabolic analysis of the Mycobacterium may identify potential targets where current or newer therapies could be directed. The approach has been partially successful already, but the cost of exploration and development is prohibitively high. There is a move towards alternate strategies including novel drug delivery systems, adjunctive immune mediation, and therapeutic vaccines [4].

There are also indications that in future, TB therapy may revolve around modulating host-immune responses, and/or reducing host inflammatory responses, concomitantly targeting bacterial survival and multiplication [1]. This type of "host-directed therapy" may involve mitigation of immunologically-mediated inflammation using corticosteroids, enhancing cell-mediated immunity, and the judicious modulation of vitamin D metabolism [1].

In the near future, better pediatric formulations of TB medications (single drug as well as fixed dose combinations) will become available. For example, within a few years of becoming available for adults, bedaquiline is now available as 20 mg pediatric tablets, and delaminid in 25 mg formulation. Pyrazinamide 150 mg dispersible tablet, levofloxacin and moxifloxacin in 100 mg dispersible tablet form, ethionamide 125 mg dispersible tablet, and cycloserine 125 mg mini-capsule, have already received WHO prequalification [24]. There is also considerable progress towards manufacture of child-friendly preparations such as orally disintegrating tablets, water dispersible tablets, syrup formulations, stable powders for suspensions, and a host of novel drug-delivery methods.

CONCLUSION

Revisiting the 50-year-old publication by Dingley and Sehgal, highlights the importance of meticulous research for treating childhood tuberculosis. The current scenario is encouraging, but far from perfect. It appears that some of the challenges encountered half a century back, persist even today (although in somewhat different forms). The future is promising if all stakeholders join hands to transform the dream of TB control, into reality.

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Novel OPV is Still not the Right Tool for Polio Eradication

The technology behind the development of the novel live oral poliovirus vaccine (nOPV) is admirable [1]. Its potential benefit is improved safety relative to that of Sabin OPV. However, in terms of usefulness for global polio eradication, is incomplete safety or low efficacy the greater problem with Sabin OPV? We believe it is the latter, which is not, and theoretically cannot be, addressed in the development of nOPVs.

The latest report of the Independent Monitoring Board of the Global Polio Eradication Initiative (GPEI) mentions that all five cases of wild virus polio in Afghanistan in 2023 were in children who had already received 16 to 28 doses of OPV and yet remained completely non-immune to wild poliovirus infection and invasion into their spinal cords [2].

The phenomenon of geographic variations of vaccine efficacy of OPV was documented in Nigeria and India prior to its adoption in the Expanded Programme on Immunisation (EPI) in 1974 [3,4]. Yet, at that time, the choice was well justified for ease of administration and low cost. In 1988, when the decision was taken to aim for eradication, exclusive dependence on OPV was not justified, more for its poor efficacy in low- and middle-income countries (LMICs) than for its incomplete safety. By then inactivated poliovirus vaccine (IPV) combined with other injected EPI vaccines was available, making it even easier for routine vaccination than OPV which entails a separate product, cold-chain space, and staff time.

It is widely recognized that low population immunity is the driving force behind the evolution and spread of circulating vaccine derived polioviruses (cVDPVs), which is by far the greater problem faced by GPEI during the last two decades. Where OPV's vaccine efficacy and vaccination coverage were high, cVDPVs did not emerge.

In Afghanistan and Pakistan, wild type 1 virus is still endemic; the hope that it could be eradicated by 2023 is unfortunately unrealizable [2]. If children develop polio despite 28 doses of OPV, the still unaddressed problem is its poor vaccine efficacy. For eradication, high vaccine efficacy is essential – and that is precisely what IPV offers.

Since the geographic variations in vaccine efficacy of OPV are not determined by the basic property of vaccine viruses, but by external factors, genetic engineering of vaccine virus cannot rectify the low efficacy. The other vaccine in hand, IPV, is far better than any live oral vaccine that could be made afresh in the laboratory. As far as we know, no child has developed polio after receiving 3 doses of IPV.

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Early Predictors of Ventilator Associated Pneumonia in Preterm Neonates Admitted in a Special Newborn Care Unit

We read with interest the original article authored by Pahwa et al in the January issue of *Indian Pediatrics* [1]. We congratulate the authors for highlighting risk factors for VAP in the most vulnerable preterm neonates. We have noticed some issues and seek clarifications. The CDC guidelines suggest doing laboratory tests in the presence of clinical suspicion for VAP. Was there any clinical suspicion in the "non-VAP group" requiring diagnostic workup? Also, CDC guidelines do not advocate use of ET tip culture [2]. We would also like to know the isolates from the non-VAP group. The methodology for collection of ET aspirates including the timings needs to clarified. The threshold at which ET aspirate quantitative cultures was considered positive is not defined. It was surprising to see the male preponderance in the study population (50 males). Were there more male neonates amongst the outborn admissions? Also, it seems that neonates were enrolled by 'convenience sampling" and not "convenient sampling"

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AUTHOR'S REPLY

We thank the authors for bringing out relevant points for discussion. The main aim of this study was to determine the early predictors of ventilator associated pneumonia (VAP) by examining the endotracheal aspirate (ETA) by microscopy and culture [1]. As per study protocol, diagnostic samples were collected by endotracheal (ET) aspiration from eligible neonates after 48 hours of mechanical ventilation, whenever suctioning was warranted. Suctioning was done only when one of the following conditions was encountered: respiratory distress worsened, visible secretions were present in ET tube, oxygen saturation fell, or diminished breath sounds were found on auscultation. The mean (SD) time from intubation to ETA collection was 53.98 (4.27) h. ET tube tip culture was considered as one of the diagnostic methods for VAP, as per study protocol. A study by Gupta et al 2017, also utilized ET tube tip culture for early detection of VAP [2]. However, we are not routinely treating neonates according to ET tube tip culture report.

In the present study, we sent the ET tube tip culture at the time of first ET tube replacement or at extubation, which ever was earlier. The mean (SD) time from intubation to ET tube tip culture collection was 72.09 (10.76) h. ET tip culture was positive in 78.7% of VAP neonates and 27.3% non-VAP neonates. The sensitivity, specificity, PPV and NPV of ET tip culture in our study was 78.7%, 72.7%, 80.4% and 70.6% respectively. *Klebsiella pneumoniae* was the most common (48.9%) isolate followed by *Acinetobacter baumanii* (12.8%).

Proper hand washing and aseptic precautions were observed during collection of ETA by open suction using a sterile feeding tube or disposable mucus extractor. If the yield was less (< 2mL), 1-2 mL of normal saline drawn from a freshly opened ampoule was instilled into the ET and collected back. The sample so collected was transported to the laboratory for microscopic analysis and culture. Samples collected in the night were stored at 4°C overnight and sent to the laboratory next morning. A smear was prepared from ETA for gram staining to determine the type of organisms.

The isolates from the non-VAP group (n =33) included *Klebsiella pneumoniae* (n =5), *Pseudomonas aeruginosa* (n = 2) and *Acinetobacter baumanii* (n = 2). No organism was isolated in 24 (72.7%) children. Culture of ETA and ET tip was done on blood and MacConkey agar and the results were expressed as colony forming units (CFU)/mL, with a threshold for diagnosing VAP as 10^5 CFU/mL. Out of 31 neonates admitted in the outborn unit, 21 were males. Participants were selected by convenience sampling.

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Reactions of ASHAs to a Decision Support Tool to Support Population Level Distribution of Iron and Folic Acid Supplements

Accredited Social Health Activists (ASHAs) from India were honored as world leaders at the 75th World Health Assembly for their efforts to strengthen the ties between the public health system and the community [1]. Also, an understanding of the challenges faced by ASHAs, such as a growing workload, insufficient training, having to run multiple programs concurrently, a lack of respect and acknowledgment from the community, were recognized. "Women in Global Health" has identified "capacity building in relation to the use of technology" as a key tactic for tackling the difficulties encountered by ASHAs [2]. The Government of Telangana has already started encouraging ASHAs to register households using smart phones. However, manual record-keeping is still used for routine follow-ups including maintaining the log of iron and folic acid tablets.

ASHAs play a key role in enabling the Jan Andolan which is central to the Anemia Mukt Bharat (AMB) strategy targeted at reduction of anemia. Since the AMB life cycle approach involves several demographic groups and dose types of iron and folic acid (IFA), ASHAs need to establish the necessary capacity to take on this challenge. With this in mind, a custom application was created that can directly integrate hemoglobin data from the auto analyzer straight from the field when the STAR trial group [3] launched a cluster randomized trial to assess the impact of a "screen and treat anemia" approach in the community [4]. This software can classify participants into distinct stages of anemia using a decision-support tool. It can also display the quantity, color, and dose of the tablets or syrup, as well as the frequency of consumption. Supporting ASHAs as the trial's intervention delivery agent was the goal of this endeavor.

A structured likert-scale was used to gather feedback from 42 ASHAs from three primary health center catchment areas in Hyderabad, Telangana, after they were shown this decision support tool. Approximately 62% (n = 26) ASHAs concurred that utilizing a digital device will lessen the workload for ASHAs. Regarding the decision support tool's ability to produce proper decisions regarding IFA distribution, roughly 38% (n = 16) ASHAs strongly agreed. 50% (n = 21) of the ASHAs thought that using the decision support tool would save them time when giving pills or syrups, and 42% (n = 18) thought it would be beneficial because they would not have to recall different doses of IFA. The majority of them believed that ASHAs' trust in implementing the program would increase while reducing the human error in determining IFA dose. With the right training, the tool can help ASHAs optimize their workflow for the roll-out of the Anemia Mukt Bharat Program and help them become digitally competent.

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Salty Diabetes: Hypernatremia in Diabetic Ketoacidosis

Hyponatremia in diabetic ketoacidosis (DKA) is an expected electrolyte imbalance secondary to dilutional effect of hyperglycemia. Hypernatremia in DKA is rarer and is associated with increased morbidity and mortality. The exact etiology for the same is not clear. Several mechanisms such as renal losses secondary to glucosuria mediated osmotic diuresis, vomiting and diarrhea and inappropriate water replacement have been proposed. Treatment consists of aggressive management of DKA instead of hypernatremia, choosing a hypo-osmolar fluid, and switching to dextrose normal saline (0.45%). We present a 14-month-old girl with DKA and severe hypernatremia who responded to aggressive management of DKA, rigorous intravenous hydration and the above-mentioned strategies.

A fourteen-month-old girl presented in altered sensorium with a history of respiratory distress and fever. She had a heart rate of 172 beats per minute, respiratory rate of 38 breaths per minute, oxygen saturation of 89% on room air, normal blood pressure and Glasgow Coma Scale (GCS) of 10 (E3V3M4). Physical examination was remarkable for a thin physique, dull activity, acidotic breathing and altered sensorium. At admission, fingerstick glucose was 511 mg/dL. Initial laboratory reports revealed a blood sugar of 545 mg/dL, pH of 6.9, lactate of 0.8 mmol/L, bicarbonate of 4.4 mEq/L, partial pressure of CO2 of 7.6 mmHg, suggestive of metabolic acidosis, with serum sodium 147 mEq/L (corrected sodium 153 mEq/L), potassium 5.2 mEq/L, chloride 110 mEq/L, and positive urine ketones. HbA1C level was 9%. There was no previous history of diabetes in the child.

The child was started on oxygen using a high-flow nasal cannula (HFNC) and received a 0.9% saline bolus. Three hours later, the sodium levels increased from 147 mEq/L to 154 mEq/L. Intravenous fluids were continued at 50 mL/hour with added potassium. Insulin infusion was started at 0.1 units/kg/h and was adjusted as required. Subsequently the corrected serum sodium of 160-166 mEq/L was recorded at 3 and 20 hours respectively (**Table I)**. Fluids were changed from 0.9% to 0.45% NS once the blood glucose was close to 250 mg/dL, to initiate the correction of sodium at a rate of approximately 0.5 mEq/L/hour. Chest *X*-ray was suggestive of bronchopneumonia. Continuous monitoring of vitals, urinary ketones, electrolytes and blood gas was done. The child received blood transfusion in view of low hemoglobin (6.2 g/dL).

The corrected sodium decreased after 30 hours to 149 mEq/L (**Table I**) with a noticeable improvement in mental status. Child was weaned off HFNC on day 2. Insulin infusion was tapered and subcutaneous insulin was started at 0.4 units/kg/day once the child was able to tolerate oral intake, mental status improved, and the anion gap resolved. She was discharged after counseling regarding the risks and complications of the disease and precautions to be taken.

Electrolyte disturbances are common in patients with diabetes and may be related to the osmotic effect of glucose that causes the fluid to shift from intracellular spaces to extracellular compartment and osmotic diuresis leading to dehydration.

Hypernatremia has been described less commonly in pediatric DKA and is usually associated with excessive soft drink ingestion [1]. Our patient did not have any similar history. Hypernatremia may ensue following the loss of water during vomiting, glucose-induced osmotic diuresis and insensible losses, which add to consequential high osmolarity. Acidosis was reported as the most influential and synergistic factor with high osmolality, dismissing the role of serum ketones in DKA with altered sensorium [2].

Normal saline is the fluid of choice in DKA with low or normal serum sodium levels [3]. It will cause intravascular expansion and correct the hyperosmolar hypovolemic hyponatremia. This is based on the consideration that every litre of normal saline can, theoretically, increase serum sodium by 0.41 mEq/L per litre of normal saline administered, assuming serum sodium of 140 mEq/L and total body water of 60%. However, in patients with hypernatremia and DKA, solutions with less sodium content, such as Ringer's lactate (RL) (130 mmol/L of sodium for every litre of the solution infused) or half normal saline (77 mmol/L of sodium for every litre of the solution infused) are more appropriate to decrease the serum sodium at an initial stage.

The rate of sodium correction is critical and suggested at 10 mEq/L per 24 hours [4]. However, the correction rate of acute hypernatremia is not as well defined as it is for acute hyponatremia. Low pH seen in DKA can cause increased proteolysis and an inability of the proteins to

Table I Electrolyte and Blood Gas Parameters During Initial DKA Management

Time since admission (h)	1	3	6	12	20	24	30
Serum sodium (mEq/L)	147	154	-	155	160	152	145
Corrected serum sodium (mEq/L)	153	160	-	161	166	154	149
Anion gap	22	26.5	26.6	19.8	17.1	27.9	16
Serum potassium (mEq/L)	5.2	5.2	3.7	3.4	4.0	4.1	4.2
SerumChloride (mEq/L)	110	119	112	111	108	107	111
Bicarbonate (mEq/L)	4.4	7.5	-	14.1	-	14.6	12.2
Blood glucose (mg/dL)	511	461	218	489	465	235	213
pH	6.92	7.15	-	7.35	-	7.31	7.32
pCO2 (mmHg)	7.6	11.9	-	20.4	-	25.9	24.6

Values are recorded levels at the respective time points

function at their physiological pH dysregulating the normal function of cells [5]. It can also decrease systemic response to catecholamines, leading to hypotension, organ dysfunction, and death if left untreated. Dehydration requires rapid management in moderate to severe hypovolemic hyperosmolar hypernatremia and may be more critical to treat.

In the index case, the treatment of DKA was prioritized followed by correction of hypernatremia to prevent a rapid change in osmolarity and cerebral edema. Altered sensorium has been attributed to the hyperosmolarity of the intravascular space that develops acutely and decreases the water content in the brain. Hypernatremia also causes altered sensorium due to cellular dehydration. In this patient, both DKA and hypernatremia contributed to the alteration in sensorium. These were identified and treated timely that improved recovery.

This case report highlights the importance of understanding the management approach required for hypernatremia and DKA to prevent complications associated with these two conditions.

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Balanced crystalloid as bolus for septic shock in children (*Crit Care Med. 2023;51:1449-60*)

This multicentre, parallel group, triple-blind, randomised controlled trial, conducted in both Pediatric Emergency Department (ED) and Intensive Care Unit (ICU), determined if initial fluid resuscitation with balanced crystalloid (e.g., multiple electrolytes solution MES, Plasmalyte) or 0.9% saline adversely affects the kidney function in children with septic shock. Children were randomized to receive fluid boluses of either MES (PlasmaLyte A) (n = 351) or 0.9% saline (n = 357) at the time of identification of shock. The primary outcome was new and or progressive acute kidney injury (AKI), defined as a rise in serum creatinine ≥ 0.3 mg/dL or 1.5 times the baseline value, or urine output ≤ 0.0.5 mL/kg/hr for 6 h, any time within the seven days of fluid resuscitation. Balanced crystalloid arm had significantly lower rates of AKI (21%) compared to 0.9% saline (33%) (RR 0.62, 95% CI 0.49-0.80, P < 0.001). The need for RRT was also lower in the balanced crystalloid group (9% vs 16%, P = 0.006). The proportion of children with hyperchlo-remia were lower in the MES versus the saline group at 24, 48, and 72 hours. ICU mortality was similar across the intervention groups: balanced crystalloid 33% vs NS 34%; RR 0.97 (95% CI [0.79-1.2]). Authors concluded that when compared to 0.9% saline, balanced crystalloid used as fluid bolus reduced AKI and improved outcomes in children with septic shock.

Properties of ultrasound-rapid MRI clinical diagnostic pathway in suspected pediatric appendicitis (*Am J Emerg Med. 2023;217-24*).

This prospective cohort study was conducted in 624 previously healthy children aged 4-17 years to determine the diagnostic accuracy of an ultrasound (US)-MRI clinical diagnostic pathway to detect appendicitis in the emergency department (ED). Children undergoing US for suspected appendicitis and clinical re-assessment were included. Children with non-diagnostic US and persistent appendicitis, or those with a discrepancy between screening US and clinical re-examination, under-went ultra-rapid MRI (US-MRI pathway), which was inter-preted as positive, negative or non-diagnostic. Cases with missed appendicitis, negative appendectomies, and CT utilization were considered clinically diagnostically inaccurate. Primary outcome was the proportion of accurate diagnoses of appendicitis/lack thereof by the pathway. The study algorithm was compared to previous studies of serial USG pathways, which were shown to be 94% accurate. They reported that 150 out of 624 (24%) children had appendicitis; 255 ultrasounds (40.9%) were non-diagnostic. Of the 139 US-MRI pathway children (after 117 non-diagnostic and 22 conclusive ultra-sounds), 137 (0.98%; 95% CI 0.96-1.00) had clinically accurate outcomes (1 CT, 1 negative appendectomy): sensitivity 100%, specificity 98.3%, positive predictive value 90.5%, negative predictive value 100%. The authors were able to demonstrate 98.7% clinical accuracy of the algorithm with a sensitivity of 98% and specificity of 98.9%. The authors concluded that the US-rapid-MRI pathway demonstrated high clinical accuracy in suspected pediatric appendicitis after an initial non-diagnostic ultrasound.

Association of prehospital transfusion with mortality in pediatric trauma (*JAMA Pediatr. 2023;177:693-9*)

This retrospective cohort study examined 559 children (< 17 years) with traumatic injuries in the last 10 years who were given blood transfusion either in the prehospital setting or the emergency department (ED). Data was retrieved from the Pennsylvania Trauma Systems Foundation Registry, catering to more than 50 trauma centers. A propensity score was employed to compare the patients who received transfusion in the two settings. 24-hour mortality was the primary outcome. Secondary outcomes included in-hospital mortality and other complications of traumatic injury such as acute kidney injury (AKI), sepsis, acute respiratory distress syndrome (ARDS). A mixed-effects logistic regression model was used to study the association between prehospital transfusion (PHT) and emergency department transfusion (EDT). The authors found that both the 24-hour mortality (16% vs 27%) and the in-hospital mortality (21% vs 32%) were significantly lower in the PHT cohort compared with the EDT cohort. The number needed to treat (NNT) to reduce 24-hour mortality was 6 (95% CI 3-10), and for in-hospital mortality was 5 (95% CI 4-10). A significant reduction in mortality was reported with PHT compared to EDT.

2023 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations: Summary From the Basic Life Support; Advanced Life Support; Paediatric Life Support; Neonatal Life Support; Education, Implementation, and Teams; and First Aid Task Forces. (*Circulation. 2023; 148:e187–e280*)

This guideline is the latest evidence-based update by the International Liaison Committee on Resuscitation (ILCOR) group, focusing on Pediatric Advanced Life Support, Basic Life Support and Neonatal Advanced Life Support. The key highlights of the guidelines are that bag and mask

ventilation is a reasonable alternative to advanced airway devices such as endotracheal intubation or supraglottic airway in out-of-hospital cardiac arrest (OHCA) in children. However, if endotracheal intubation is required, cuffed tubes are preferred. They recommended continued emphasis on administration of intravenous epinephrine within 5 minutes of initiation of chest compression, irrespective of the setting. Either amiodarone or lidocaine may be used for shock refractory ventricular fibrillation or pulseless ventricular tachycardia. Extracorporeal Cardiopulmonary Resuscitation (CPR) may be considered for pediatric patients with cardiac diagnoses refractory to conventional CPR for in-hospital cardiac arrest in settings with existing extracorporeal membrane oxygenation (ECMO) protocols, expertise, and equipment. Regarding postcardiac arrest targeted temperature management (TTM), the guideline re-emphasise TTM during postcardiac arrest care for optimal outcomes. Regarding neuroprognostication after Return of Spontaneous Circulation (ROSC) they recommended that pupillary light reflex and normal plasma lactate (< 2 mmol/L) within 12 hours post ROSC may predict good neurological outcomes in children after cardiac arrest; neuroimaging i.e., CT at 24-48 hours and MRI between 72 hours to 2 weeks may be helpful for neuroprognostication; a reactive EEG between 6-72 hours post-ROSC may predict good neurological outcomes. Other EEG characteristics may also be helpful, such as the presence of sleep spindle sleep II architecture at 12-24 hours.

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NEWS IN BRIEF

The new Butantan Dengue Vaccine

The dengue virus infects 390 million people annually and has so far eluded elimination by man. Each new vaccine against this scourge has exposed new complexities of the immune response to this virus. The Instituto Butantan in Brazil recently published results of a phase 3 trial of a new dengue vaccine. Overall, 2-year efficacy rates were 80% in previously unexposed participants and 89% in those with previous dengue exposure. This live attenuated vaccine has been tested on more than 16,000 participants in Brazil with ages ranging from 2-59 years. How does this vaccine compare to the 2 vaccines developed previously, namely Dengvaxia (Sanofi Pasteur) and Qdenga (Takeda)?

Dengvaxia is a 3-dose vaccine which was developed using the yellow fever virus. It was approved first in 2015 after phase 3 trials and a single season of disease surveillance. In the third year after vaccination, it was noted that children who had been unexposed to dengue prior to vaccination developed severe dengue and increased rates of hospitalization. There was a huge outcry especially in the Philippines and the vaccine license was revoked in that country. Since then, this vaccine is licensed for use only in children above 9 years of age, preferably with previous known exposure to dengue.

The Japanese Takeda vaccine is a 2-dose vaccine and has shown good efficacy against DENV-2 in immune and non-immune participants. However, it had only moderate efficacy against DENV-1. There is also a suggestion of increased hospitalization after DENV-3 infections in seronegative vaccinated individuals. It is approved above 4 years of age in people irrespective of previous dengue exposure.

The new Butantan vaccine is a single dose subcutaneously administered vaccine and has shown good efficacy against DENV-1 and 2 serotypes. Efficacy against DENV-3 and 4 could not be assessed due to low circulation of those serotypes during the trials possibly due to the Zika virus epidemic during that time. Patients will be monitored for a total of 5 years to identify any possible late effects. The holy grail of efficacy and safety in the dengue vaccine appears closer though still a little out of reach so far. (*Kallás EG, Cintra MAT, Moreira JA, et al. Live, attenuated, tetravalent Butantan–Dengue Vaccine in children and adults. N Engl J Med. 2024;390:397-408*.)

Antibiotic Prescriptions Must Mention Indication

Dr Atul Goel, Director General of Health Services, has urged all doctors to mention the indication for antibiotics on their prescription. Pharmacists have also been advised to dispense antibiotics only if a valid prescription is available. The move has come after a survey by the National Centre for Disease Control. These surveys have started after the WHO developed the Global Point Prevalence Survey methodology to monitor antibiotic use and misuse. The AWaRe classification of the WHO has 3 important categories- "**A**ccess" group of antibiotics like cotrimoxazole or amoxycillin-clavulanic acid which may be used against a wide range of common infections. The "**Wa**tch" group which have antibiotics like amikacin and piperacillin which have a higher risk of antibiotic resistance and may be used carefully when required. The "**Re**serve" group has antibiotics like colistin and linezolid and may be used only in multi-drug resistant organisms. There is a last group of "**Non-indicated"** antibiotics which include drug combinations which have not been shown to be effective such as ampicillin/cloxacillin and piperacillin/sulbactam. The aim is to have 60% or more in "access" group. In our national survey of 12,000 prescriptions between 2021-2022 over 20 tertiary care centres in India 38% were in "access" group, 57% in "watch" group, 2% in "Reserve" group and 3 in "not recommended" group. In admitted pediatric patients 68% were on antibiotics. Overall, 53% were on more than one antibiotic and 4.6% on four or more antibiotics. More than half were on prophylactic antibiotics. The simple act of writing an indication in each antibiotic prescription will make doctors more mindful and may help reducing the menace of antibiotic resistance which is a leading challenge in health care today. (*Indian Express. January 20, 2024*; *https://www.downtoearth.org.in/news/health/over-half-of-prescribed-antibiotics-in-india-can-lead-to-amr-finds-national-centre-for-disease-control-93715*)

Elon Musks' Neuralink

The tweet from Elon Musk on January 30, 2024 received 56 million views. The first human has been implanted with Neuralink and shows promising results. What is Neuralink? What are the implications and how does the scientific community view these developments? Neuralink is a brain-computer-interface (BCI) which consists of a chip and more than 1000 flexible fibres which are implanted into the brain. It differs from previous BCIs because it is wireless and works using blue tooth and it measures intraneuronal spike potentials. The aim is to identify thoughts related to motion and subsequently translate them into either text or movements. Previously the goals of BCI's have been been stated as "We have modest goals. We want to make the blind see, deaf hear and the paralyzed move!"

The FDA approved human trials in May 2023, and the company opened enrolment in September 2023 for people with quadriplegia. Previously the company was under federal investigations for more than 1500 animals which were killed during animal trials. Scientists are uncomfortable because the trial is not registered under *ClinicalTrials.gov* and there is no transparency of the study protocol or results. The heady combination of science and immoderate wealth need prudence and wisdom to avoid catastrophes. (*https://www.nature.com/articles/d41586-024-00304-4*; *https://www.scientificamerican.com/article/elon-musks-neuralink-has-implanted-its-first-chip-in-a-human-brain-whats-next/*)

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Thought of one-Removed two

A seven-year-old child brought to casualty with dysphagia, drooling of saliva and chest pain since an hour. Chest *X*-ray showed a single rounded opacity in the upper oesophagus **(Fig. 1A)** hence, pharyngo-gastroscopy was done immediately. There were two coins similarly aligned impacted in the upper oesophagus **(Fig. 1B)**. Two coins were removed successfully with rat toothed forceps curing the child's ailments **(Fig.1C, 1D).**

Foreign body ingestion is a great diagnostic conundrum for clinicians. The ingestion of multiple coins by children is rare; moreover, only three other cases of multiple coin ingestion with perfect alignment on *X*-ray have been reported. Chest or abdominal radiography should be the first investigation of choice however, it has its own limitations like missing the radiolucent objects and counts of object in case of perfect alignment. Meticulous endoscopic examination should be done to ensure removal of suspected foreign bodies and to avoid second look endoscopy during foreign body extraction.

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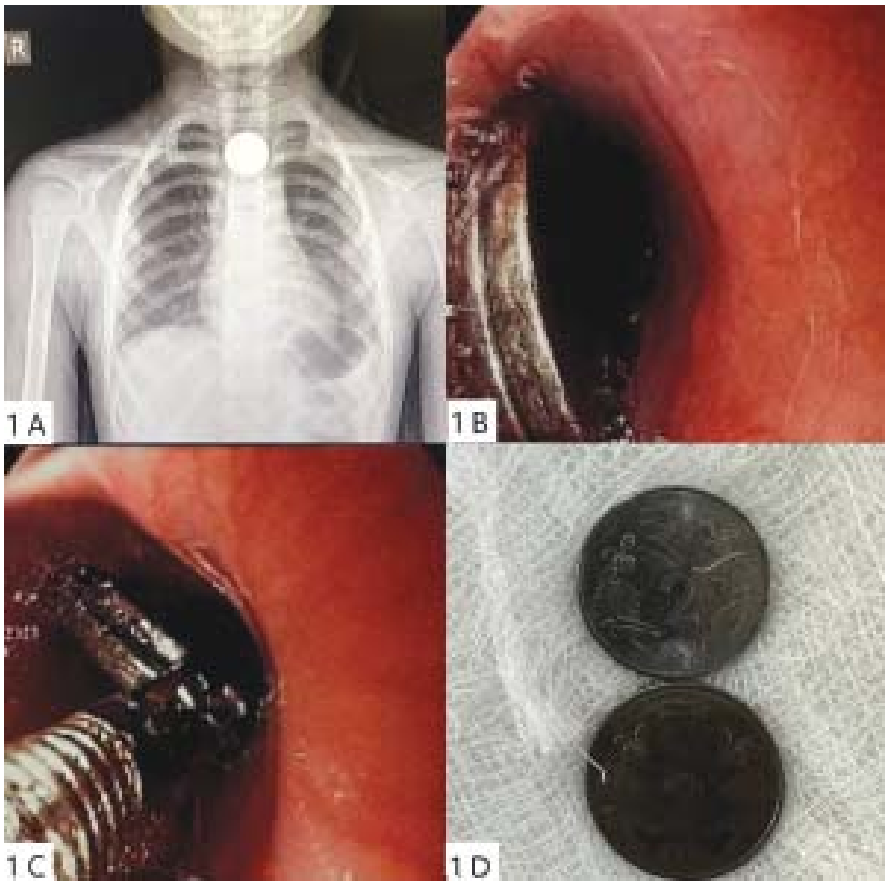

Fig.1 A Chest *X*-ray (posterior view) showing a rounded foreign body, B Endoscopic picture of two impacted coins, C endoscopic removal of the coins rat tooth forceps, D Two coins of two each after removal

Meconium Pearls in a Newborn

A bucket-handle anorectal malformation was detected in a male newborn weighing 3200g at birth. Dark green appearing thin-walled cysts were seen along the midline raphe in continuity with the dysplastic anal aperture. These were not associated with inflammatory features and existed along the midline raphe (**Fig. 1**). The newborn was treated with anoplasty and serial dilatation of the anal cavity. No perineal or intra-pelvic fistulous communication was seen. The infant had an uneventful follow-up and meconium pearls had disappeared.

Meconium pearls are greenish meconium filled cystic swellings which are typically associated with low anorectal malformation. These represent a partially obliterated subcutaneous primitive tract connected to the malformed anal cavity in the perineum via an ectopic fistula during fetal life. The presence of meconium pearls should prompt a needful exploration of the perineal fistula. A differential diagnosis of midline raphe cyst (midline raphe closure defect) should be considered when the cysts persist to a higher age.

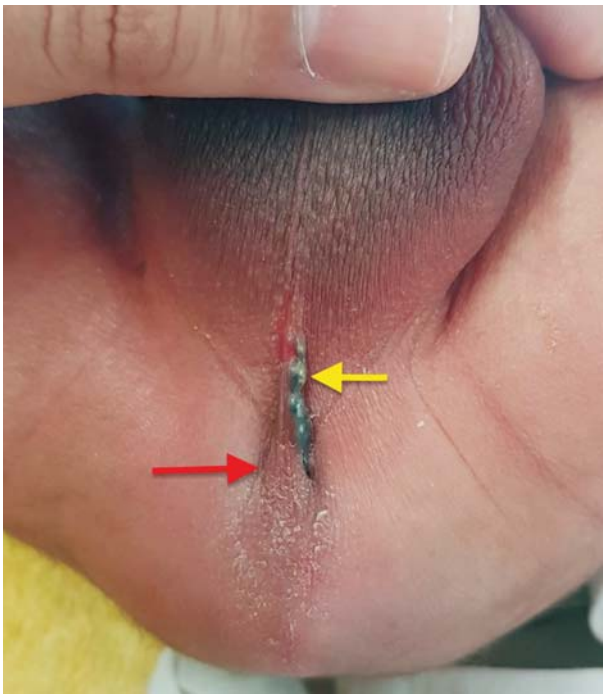

Fig. 1 Bucket-handle anorectal malformation (red arrow) and midline meconium pearls (yellow arrow).

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Cydnidae Pigmentation

An 8-year-old girl presented during the monsoon season with asymptomatic brownish spots on her soles for two days duration. There was no history of associated fever, preceding skin eruption, or contact with exogenous chemicals. Her father recalled that the girl had played barefoot in a park they had visited recently. Examination revealed multiple, haphazardly arranged, round/oval reddish-brown macules with tapering edges bilaterally over the soles (**Fig. 1**). A diagnosis of cydnidae pigmentation was made, and parents were reassured of the benign condition. After one week, the lesions disappeared without any residual marks.

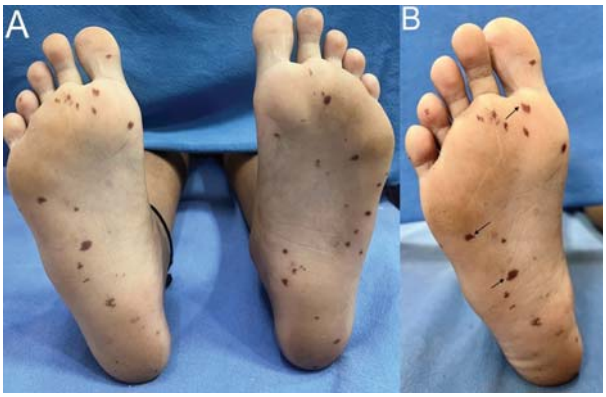

Fig. 1 A) Multiple, haphazardly arranged, reddish-brown macules bilaterally over the soles, **B**) Lesions with round/oval with tapering edges.

Cydnidae, also known as "burrowing bugs", release a malodorous hydrocarbon produced in specialized glands as a defense mechanism in response to stress. On accidental crushing of these bugs, this secretion results in the appearance of characteristic pigmentation over the contact site. Clinical pointers like abrupt onset, appea-rance during the rainy season, history of barefoot activity, and presence of pigmented macules with streaky ends on exposed body parts help differentiate it from other conditions like acral

lentigines, petechiae of dengue fever, etc. Awareness among physicians can help avoid invasive investigation in such conditions, and proper counselling regarding its self-resolving nature will reduce parent/patient's anxiety and stress.

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Bathing Suit Ichthyosis

A 5-year-old girl, product of a consanguineous marriage, was evaluated for congenital ichthyosis. Despite being a collodion baby at birth, she developed restrictive scales on the trunk by two months of age. Notably, these scales intensified during the summer months but remained mild in winter. Upon examination, dark brown lamellar scales were predominantly found on the trunk, neck and axillae sparing the limbs and face. (**Fig. 1**). A skin biopsy revealed orthohyperkeratosis of the epidermis, a normal granular layer with a mild inflammatory infiltrate in the dermis, consistent with proliferative ichthyosis. Genetic investigation identified the mutation c.944 G>T of TGM1 gene in exon 6 of chromosome 14. The diagnosis of bathing suit ichthyosis was established, and the patient showed mild improvement with topical emollients and topical keratolytics.

Bathing suit ichthyosis, a rare variant of autosomal recessive congenital ichthyosis, is nonsyndromic and regarded as a temperature-sensitive phenotype. Differential diagnosis includes other types of generalized lamellar ichthyosis and congenital ichthyosiform erythroderma. Syndromic ichthyosis such as Netherton syndrome and Sjogren Larsson disease could also be suspected but are ruled out due to the absence of extracutaneous involvement in bathing suit ichthyosis. The condition is primarily attributed to mutations in the TGM1 gene, and treatment focuses on emollients and topical keratolytics.

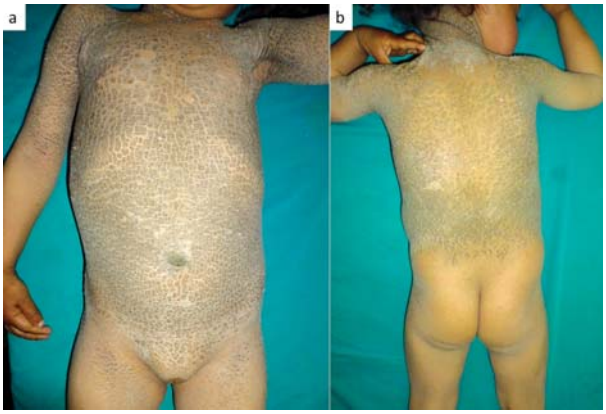

Fig. 1a. Brown lamellar scales located on the trunk, axillae and proximal upper and lower limbs; **1b**. Brown lamellar scales involving the back but sparing the buttocks

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Isolated Severe Congenital Penile Torsion of 180 Degrees

Penile torsion is a rare congenital rotational defect of the penile shaft and glans on the longitudinal axis, usually in a counter clockwise direction, that is often associated with hypospadias and chordee, rarely it can be observed as an isolated entity. While most patients are asymptomatic, rotations > 45° are associated with cosmetic and functional micturition problems.

A 12-year-old uncircumcised boy presented with difficulty in passing urine due to an upward voiding stream and discomfort during erection, observing a 180º isolated penile torsión (**Fig. 1a**). Under general anesthesia and penile block, a circumferential subcoronal incision was taken and the penile skin and dartos were degloved to the penile root with final skin over correction on the shaft of the penis (**Fig. 1b**). Postoperative course was uneventful. In severe isolated penile torsion the least-invasive approach, such as degloving and skin over correction, is a suitable option with satisfactory results.

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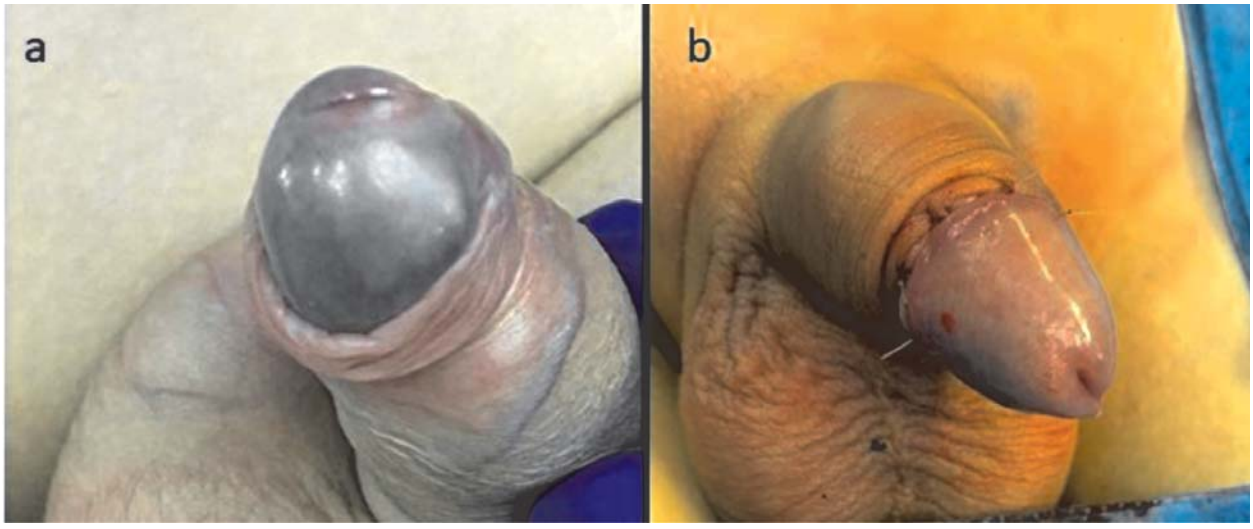

Fig. 1a 180º Isolated penile torsión , **1b** Shaft of the penis after skin over correction

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