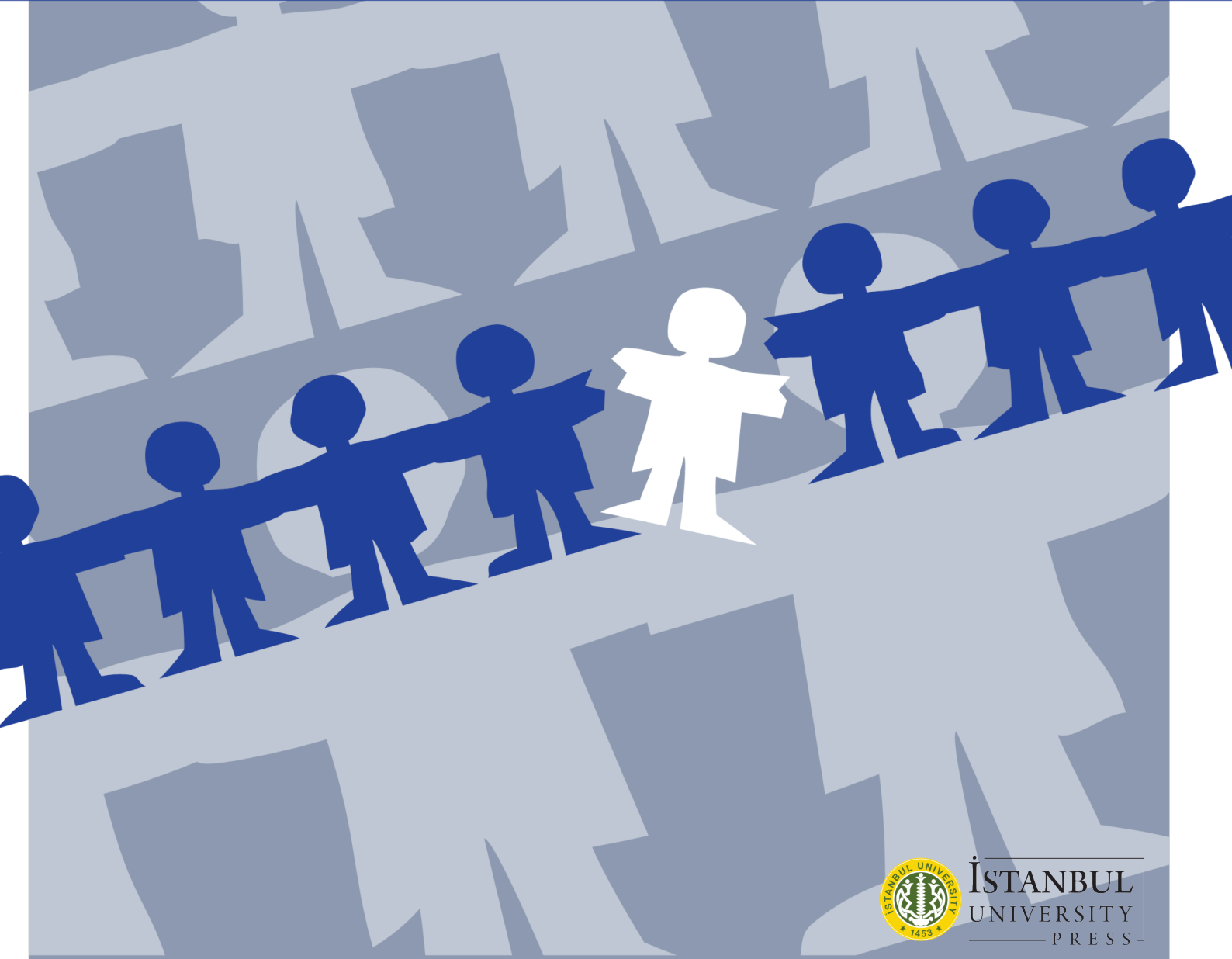


Çocuk Dergisi Journal of Child

Volume 25 • Issue 1 • March 2025



İSTANBUL
UNIVERSITY
PRESS

Çocuk Dergisi Journal of Child

Volume 25 • Issue 1 • March 2025

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Web of Science – Emerging Sources Citation Index
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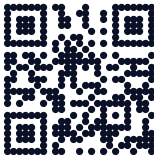
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🌐 <https://dergipark.org.tr/en/pub/jchild>

Publisher İstanbul University Press
🏠 İstanbul University Press, İstanbul University Central Campus, 34452
Beyazıt, Fatih, İstanbul, Türkiye
☎ +90 (212) 440 00 00
✉ iupress@istanbul.edu.tr
🌐 <https://iupress.istanbul.edu.tr/>

Publication Type Periodical



Authors bear responsibility for the content of their published articles.

The publication language of the journal is English.

This is a scholarly, international, peer-reviewed and open-access journal published quarterly in March, June, September and December.

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Çocuk Dergisi Journal of Child

Submitted: 11.04.2024
Revision Requested: 25.02.2025
Last Revision Received: 27.02.2025
Accepted: 05.03.2025

Research Article

Open Access

Effect of Prebiotic-Added Foods on Infant Health: A Systematic Review and Meta-analysis of Randomized Controlled Trials



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Abstract

Objective: In cases where breastfeeding is not possible, one of the recommended strategies to change the composition of the nutritional baby's gut microbiota and bring it closer to breastfed infants is to enrich the infant's food with prebiotics. The aim of this study was to systematically review the results of its effect on growth, gait and gastrointestinal (GI) system in infants fed with prebiotic-added formula and to perform a meta-analysis of the available evidence.

Materials and Methods: The literature review for this systematic review was conducted between January and February 2023 using five electronic databases: PubMed, CINAHL, Scopus, WOS and ULAKBİM. Articles were scanned using MeSH-based keywords. Only Randomized Controlled Trials conducted in the last five years were included. The data were analyzed using the Review Manager computer program (Version 5.3).

Results: The analysis included six studies involving 1399 formula-fed infants. In the post-intervention analysis of the included studies, there were no significant differences in weight (SMD: -0.21 95% CI: -0.45 to 0.03, Z=1.68, p=0.09), stool frequency (SMD:0.34 95% CI:-2.89 to 3.58, Z=4.58, p=0.84), but there was a significant difference in the stool consistency (SMD:-0.50 95% CI:-0.73 to -0.27, Z=4.24, p<0.00001).

Conclusion: This systematic review and meta-analysis confirmed that prebiotic-enriched infant formulas are likely to provide benefits for healthy infants. The studies indicate that the inclusion of prebiotics in formulas improves stool consistency. However, no significant effects were found on growth or stool frequency. These findings suggest that further research is needed to better understand the effects of prebiotics on infant gastrointestinal health.

Keywords

Prebiotics • formula • newborn • anthropometric • gastrointestinal symptoms



Citation: Tanrıverdi, D. Ç., Karaahmet, A. Y. & Bilgiç, F. Ş. Effect of Prebiotic-Added Foods on Infant Health: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Çocuk Dergisi–Journal of Child 2025; 25(1): 1-9. DOI: 10.26650/jchild.2025.1583034

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INTRODUCTION

Breastfeeding and nutrition with human milk are the source of nutrition of choice for infants and have been proven to provide a range of short- and long-term benefits for the infant's nervous, immune, metabolic, and GI system (1). Where breastfeeding and nutrition with human milk are not possible or are interrupted, breast milk counterparts should aim to provide nutritional and functional properties as close as possible to breast milk (2,3).

It has been reported that breastfeeding is beneficial for colonization in the intestines of babies after birth (4). While the composition and function of the gut microbiota play vital roles in digestion, metabolism, and activation of the immune system in infants, all of these affect the later stages of life (5,6). Prebiotics are the third most common component of breast milk; in cow's milk and infant formula, it is significantly less than breast milk (7). In cases where breastfeeding is not possible, one of the recommended strategies to change the composition of the nutritional baby's gut microbiota and bring it closer to breastfed infants is to enrich the infant's food with prebiotics (8). Infant formula supplemented with prebiotics is reported to reduce a more adult-like microbiota diversity, reduced atopic eczema, and the occurrence of inflammatory bowel diseases in adulthood (7). In the literature, the evidence for the infant health outcomes of prebiotic-enriched formulas is limited.

MATERIALS AND METHODS

In this study, it was aimed to systematically review the results of its effect on growth, feces and GI system in prebiotic-added formula-fed infants and to perform a meta-analysis of the available evidence. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) was complied with in the preparation of the systematic review and meta-analysis (9).

Eligibility Criteria

The following criteria (PICOS) were considered in the selection of the studies to be included in the study:

Participant (P): Healthy infants. The infants included in the study had the following criteria for inclusion. (1): 0-6 months old and (2) formula-fed infants.

Intervention (I): Prebiotic-added food.

Comparison(C): (1) Placebo (2) Breastfed infants reference group (3) Formula without prebiotics.

Outcomes (O): (1) Anthropometric measurements (2) Stool characteristics (3) Gastrointestinal characteristics.

Study design (S): Double-blind, randomized controlled trials, placebo, and controlled groups were included. Articles given prebiotics, preterm, with health problems were excluded from traditional and systematic reviews were not included.

Search strategy

The literature review was conducted between April and May 2023 using five electronic databases (PubMed, CINAHL, Scopus, WOS and ULAKBİM). The keywords were "baby" OR "newborn" OR "infant" AND "formula" AND "prebiotic" AND "anthropometry" AND "stool" AND "gastrointestinal symptoms". In order to avoid bias, the articles determined as a result of the screening were examined independently by the same researchers to determine that the analysis met the inclusion and exclusion criteria, and the full texts of the studies that were not defined in the abstract were evaluated. In studies where consensus could not be reached, the researchers thought of working together. A data extraction tool developed by the researchers was used to obtain the research data.

For analysis, the effects of prebiotics on anthropometric measurements were collected as the primary outcomes, and stool characteristics and GI symptoms as the secondary outcomes.

The data analysis

Using data from the included studies, a between-group meta-analysis was conducted using continuous data and random effects models to compare the outcomes of the prebiotic supplemented formula intervention with those of the control group. When included studies assessed outcomes using the same methods, the mandala painting intervention was measured using the mean difference (MD) with 95% confidence intervals (95% CI). When the included studies used different methods, the mandala painting intervention was measured using the standard mean difference (SMD) with 95% confidence intervals (95% CI). The SMD was interpreted according to Cohen's thresholds: insignificant (<0.2), small (0.2 to <0.5), moderate (0.5 to <0.8), and large (>0.8). All statistical analyses were performed using the Review Manager software (RevMan, version 5.4.1; The Cochrane Collaboration, Copenhagen, Denmark). The significance level was set at $p < 0.10$ and $p < 0.05$ for all other analyses. The evidence quality for each outcome was evaluated using the GRADE approach.

RESULTS

Literature review

The PRISMA flowchart for the literature review and selection is summarized in Figure 1. The electronic database search

and hand-search yielded 309 potentially relevant studies. After removing duplicate articles, 295 article titles and abstracts were scanned. Titles and abstracts were read to identify the relevant articles; 168 articles were removed because they did not meet the criteria for review articles, protocols, duplications, different populations, and inclusion. The remaining 127 full texts were evaluated for eligibility. Six RCT articles were included in the quantitative synthesis because they met the desired criteria (Figure 1).

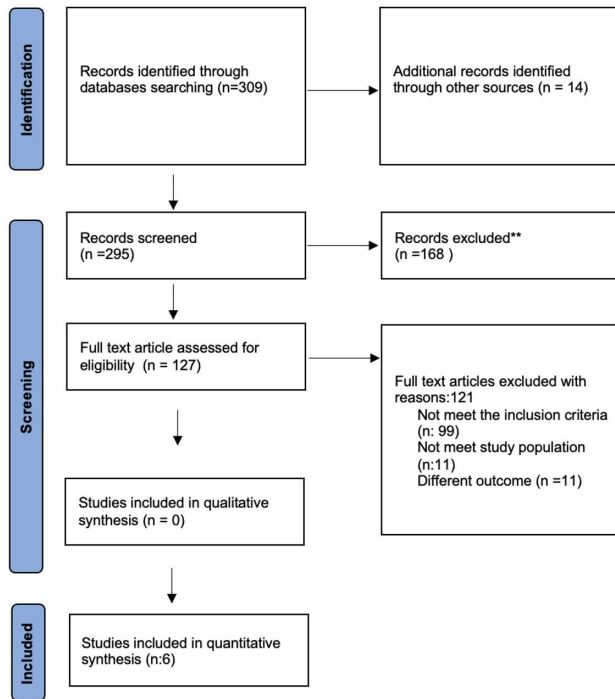


Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Study characteristics

This systematic review and meta-analysis included six studies involving 1399 formula-fed infants to assess the health outcomes of prebiotic-supplemented formula-fed infants (10-15). All studies included in the meta-analysis were double-blind RCT studies.

All of the infants included in the study were formula fed or had a requirement that their parents intended to feed them formula (10-15). The properties of prebiotics added to foods in the articles included in the study; short-chain galacto-oligosaccharides (scGOS) and long-chain fructo-oligosaccharides (lcFOS) (13), short- and long-chain inulin-type oligosaccharides to their formulas (12), polydextrose and galactooligosaccharides (10), short-chain galacto-oligosaccharides and long-chain fructo oligosaccharides

, (15) scGOS/lcFOS and large, milk phospholipid-coated lipid droplets (14) polydextrose and galacto-oligosaccharide (11).

All of the babies included in the sampling were healthy and within normal growth limits, with no health problems between 14 days and 4 months. The babies included in the study were followed between 4 and 12 months. In all of the studies, stool characteristics and anthropometric measurements were evaluated and GI symptoms (12-15), sleep and baby behavior formula (10,12,13) (Table 1).

Outcomes

Effect of prebiotics on anthropometric measurements

In the two studies analyzed, the authors reported results on weight, height and head circumference before and after treatment. The combined results of the intervention and control groups in the pretreatment period of the studies are given in Figure 2a. There was no significant difference in weight (SMD: 0.11, 95% CI: -0.13 to 0.35, Z=0.89, p=0.37). There was a significant difference in height (SMD: 0.21, 95% CI: -0.03 to 0.45, Z=1.73, p=0.08). There was no significant difference in head circumference (SMD: -0.76 95% CI: -2.16 to 0.63, Z=1.08, p=0.28).

The combined results of the intervention and control groups in the post-treatment period of the studies are given in Figure 2 b. There were no significant differences in weight (SMD: -0.21 95% CI: -0.45 to 0.03, Z=1.68, p=0.09), height (SMD: -0.05 95% CI: -0.49 to 0.39, Z=0.24, p=0.81) and head circumference (SMD: 0.27 95% CI: -0.27 to 0.82, Z=0.98, p=0.33) (Figure 2a-b)

Effect of prebiotics on the growth gap

In one study, the authors reported the results of weight, height, and head circumference before and after treatment. In the study, there was a significant difference in weight (SMD: -0.56 95% CI: -0.85 to -0.26, Z=3.71, p=0.0002) between the groups. There was no significant difference between the groups in terms of height (SMD: 0.20 95% CI: -0.09 to 0.49, Z=1.35, p=0.18) and head circumference (SMD: 0.04 95% CI: -0.25 to 0.32, Z=0.25, p=0.80) (Figure 3).

Effect of prebiotics on the stool frequency

In the two studies examined, the authors reported the results for stool frequency before and after treatment. The combined stool frequency results of the studies showed a significant difference between the groups in the pre-treatment period (SMD: -1.27 95% CI: -1.76 to -0.78, Z=9.06, p<0.00001) and after treatment (SMD: 0.34 95% CI: -2.89 to 3.58, Z=4.58, p=0.84) (Figure 4 a-b).

Table 1. Patient demographic data, symptoms, comorbidities, and associated cranial nerve palsy

Reference Country	Study design	Population	The inclusion and exclusions criteria	Protocol	Comparisons	Drop out	Outcome	Results
Rodriguez et al., 2019; Italy, Spain	Cift Blind, Multicenter, RCT*	200 babies (EG*: 94; CG*: 105; BRG*: 100)	-≤28 days of term (37≥ and ≤42 GW*), Normal birth weight (10-90 percentile), Infants within +/-2 SD relative to head circumference were included. Cow's milk and soy allergy, known to have an increased risk of lactose intolerance, having any medical condition, or having a diabetic mother baby Infants who were previously fed an IF* containing is probiotics or simbiotics were not included.	- EG* infants IF* scGOS* and lcFOS 9* added The first visit occurred at ≤28 days of age, and the infants were then assessed at 4, 8, 13 and 17 weeks (5 visits) - Measurements were made at each visit.	Control: Placebo	EG*: 22; CG*: 25 BRG*: 28	GI* symptoms, growth, stool characteristics, sleep and crying behavior, AE*	No significant difference was observed in parent-reported GI symptoms. BRG* was closer and EG* stool consistency was softer than the control group. Daily weight gain was equivalent to BRG* close growth results for each formula group. There was no clinically significant difference in AE except for the lower prevalence of infantile colic in CG* versus EG*
Neumer et al., 2021 Spain, Belgium	Dual Blind, Multi-Center, RCT*	160 babies (EG*: 81; CG*: 79)	-0-4 months old, Normal birth weight (10-90 percent according to current growth charts), - Term birth (≥37≤ and 42 weeks gestation) was included. -Parents who do not comply with the work follow-up -The presence of any related disease, any condition related to the immune system, which may affect the nutrition and growth of the B midwife, is an infection for 7 days before entering the study Infants who were fed a baby food (IF) containing probiotics or synbiotics before entering the exercise were also excluded from participation.	-EG* infant rIF* short and long chain inulin-type oligosaccharides were added. -Dlasted from the day of the abortion until the baby was one year old The basic visit took place at 0-4 months of age, and the infants were then assessed at 2,4,6,9 and 12 months of age (5 visits)	Control: Placebo	EG*: 20; CG*: 17	GI* symptoms, growth measurements, microbiota analysis, AE*	The mean duration of infection was significantly lower in infants fed P-rebiotics. Babies who received prebiotic formula had softer stools.
Colombo et al., 2021; USA*	Dual Blind, RCT*	161 babies (EG*: 79; CG*: 81)	-14-35 days old, with a height weight of ≥2500 g and a normal growth history -37-42 GW* and individual infants were included. A history of prenatal illicit drug use or clinically significant psychiatric illness; -A history of metabolic or chronic illness or food intake or congenital malformation in the B infant, -B A history of bending difficulties or food intolerance; -Immunodeficiency -Infants with planned use of p-robiotics during the study period were excluded.	-EG* infants' formulas have been supplemented with povidex and galacto-oligosaccharides -Beginner Level (14-35 days), randomization according to the study formula (4-8 days after Basic Level), 70. Day (±7 days) and 112. Corresponds to the day (±7 days). -Basic diary and actigraphy data were taken and participants were assigned to a working formula group.	Control: Does not contain prebiotics IF*	EG*: 14; CG*: 16	Bis the behavioral state and sleep-wake of the midwife, antropometri and stool characteristics	The average duration of the crying/restlessness episodes was similar in the beginning, 70. It was significantly shorter for PDX/GOS* per day and Control and was 112. It continued in the day. Day 112 Cortisol wake-up response 70th and 112th Shown in days. Significant differences in fecal microbiome beta diversity and individual taxon abundance were observed in the PDX/ GOS* group.

Reference Country	Study design	Population	The inclusion and exclusions criteria	Protocol	Comparisons	Drop out	Outcome	Results
Wang et al., 2021, China	Dual Blind, Multi-Center, RCT*	224 babies (EG*: 112; CG*: 112; BRG: 53)	• Healthy, term and ≤44 days, - 10th -90th birth weight in the percentile, - Infants without current or previous illness/condition were included. - Fully breastfed -Infants using different IF* were not included.	-EG* IF*, scGOS/lcFOS,9:1* and a symbiotic mixture of Bifidobacterium were given with the formula of partially-hydrolyzed protein (pHF). Infants were assessed at (V1), 4 (V2), 8 (V3), 13 (V4) and 17 (V5) weeks during study visits. - After the first visit, parents filled out a 7-day form before each visit, covering IF* intake, GI* symptoms, and general condition.	Control: Does not contain prebiotics IF*	EG*: 27; CG*: 22; BRG*: 2	GI* symptoms, Amsterdam Stool Scale, anthropometric measurements	EG* showed equivalence in daily weight gain (achievable outcome) between BRG* and CG*. There were no clinically significant differences in GI* tolerance or AE between the formula groups.
Teoh et al., 2022, Singapore	Dual Blind, RCT*	EG1*:155, EG2*:152, CG*:146 * BRG: 67	• have Chinese, Malay or Indian ethnicity, 37-42 GW, ≤ 28 days -According to the Fenton growth chart, the eastern weight and head circumference are between the 3rd and 90th percentile. -S-weighted term infants were included. -Diseases that may prevent work, -Special dietary needs, - Infants with all the time atitis B or HIV were not included.	-A specific prebiotic mixture scGOS/lcFOS* and a prebiotic mixture containing large, milk phospholipid-coated lipid droplets were added to the formulas of the infants in the intervention group -Zwas performed at the age of 4, 8, 13 and 17 weeks. Daily study product intake, GI* symptoms, and stool characteristics were recorded by parents for the 7-day period prior to each individual	Control: Does not contain prebiotics IF*	EG1*:27, EG2*:117, CG*: 117, BRG*: 1	GI symptoms, Amsterdam Stool Scale, anthropometric measurements	EG2* and CG* were shown to be equivalent in daily weight gain. There were no differences in secondary growth outcomes between clinically relevant groups in terms of tolerance outcomes or the number, severity, or relationship of adverse events.
Hoffman et al., 2019, USA*	Double blind, Parallel Group, RCT*	142 babies (CG*: 47; ARA-25*: 48; PDX/GOS*:47)	• 10-18 days of age, with a ≥ weight of 2500 g, -Fed only with formula at least 24 hours before R andomization, -37-42 GW and individual infants were included. -Gida retrieval, normal growth and development, or a history of a disease or congenital malformation, -Intolerance to milk-based formula during K usma or randomization, - InR-andomization, <95% of the net birth weight and older infants were excluded from a diabetic mother according to the gestational age of the child at the time of birth.	-EG* infants' IF* PDX/GOS* prebio was broken down and different concentrations of ARA* and DHA* were added -Bbabies were randomized into three groups. -Blood and saliva samples and anthropometric measurements were taken from all babies. The infants were followed until they were 14 and 120 days old.	Control: Does not contain prebiotics IF*	CG*:16, ARA-25*:17, PDX/GOS*:27	In Buccal Epithelial, PL*, RBC, anthropometric measurements, stool and gas properties	There were no statistically significant group differences in the growth rates of weight, length or head circumference. No significant group differences were detected in the frequency (number/day) of stool frequency. no significant group differences in stool consistency were detected on days 60, 90 and 120 On day 3, precursory differences in stool consistency were detected between the PDX/GOS* and CG* or ARA-25* groups.

ARA-25: arachidonic acid, DHA: docosahexaenoic acid and prebiotic mixed food. PDX/GOS: polydextrose galacto-oligosaccharides, PL: phospholipids, RBC: Red Blood Cell, scGOS: short chain galacto-oligosaccharides, lcFOS: long chain fructo-oligosaccharides, BRG: breastfed reference group, EG: Experimental Group, CG: Control Group, GI : Gastrointestinal, GW: Gestation Week, IF: Infantile Formula, RCT: Randomized Control Trial

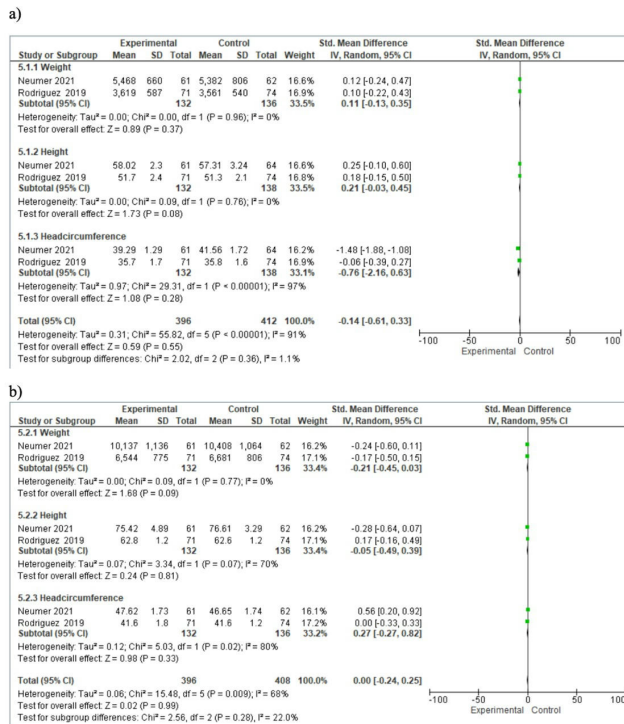


Figure 2. Meta-analysis results on the effect of prebiotics on the anthropometric measure. (a) Pre-intervention (b) Post-intervention

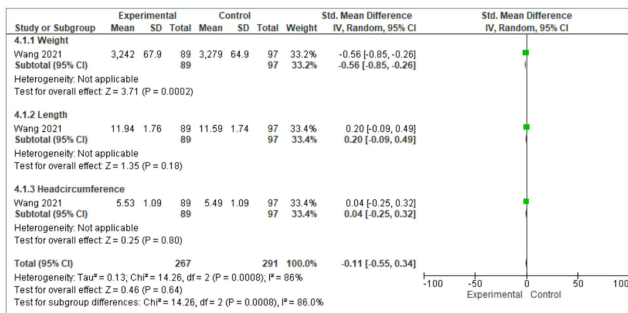


Figure 3. Meta-analysis results on the effect of prebiotics on the growth rate

Effect of prebiotics on the stool consistency

In one study reviewed, the authors reported results for stool consistency before and after treatment. Stool consistency results were significantly different between the groups in the pre-treatment period (SMD:-0.49 95% CI:-0.72 to -0.26, $Z=4.13$, $p<0.00001$) and after treatment (SMD:-0.50 95% CI:-0.73 to -0.27, $Z=4.24$, $p<0.00001$) (Figure 4 a-b).

Gastrointestinal Symptoms

In one study reviewed, the authors reported the results of vomiting and regurgitation related to GI system symptoms. The results of vomiting were found to be no significant difference between the groups in the pre-treatment period (SMD:-0.05 95% CI:-0.27 to 0.17, $Z=0.45$, $p=0.65$) and after treatment (SMD:0.00 95% CI:-0.01 to 0.01, $Z=0.00$, $p=1.00$). The results

of regurgitation were found to be no significant difference between the groups in the pre-treatment period (SMD:-0.13 95% CI:-0.63 to 0.37, $Z=0.51$, $p=0.61$) and after treatment (SMD:-0.03 95% CI:-0.12 to 0.06, $Z=0.65$, $p=0.52$) (Figure 5 a-b).

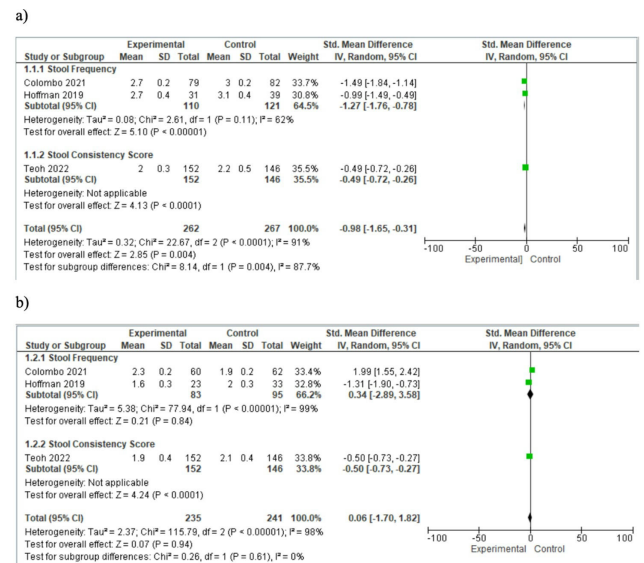


Figure 4. Meta-analysis results on the effect of prebiotics on the stool characteristics: (a) Pre-intervention (b) Post-intervention

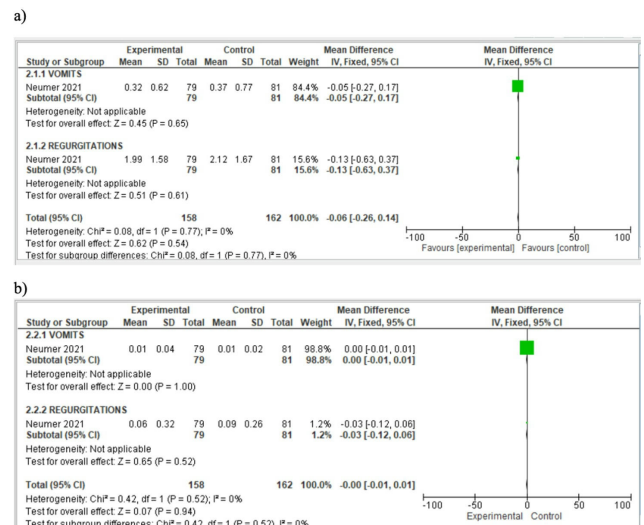
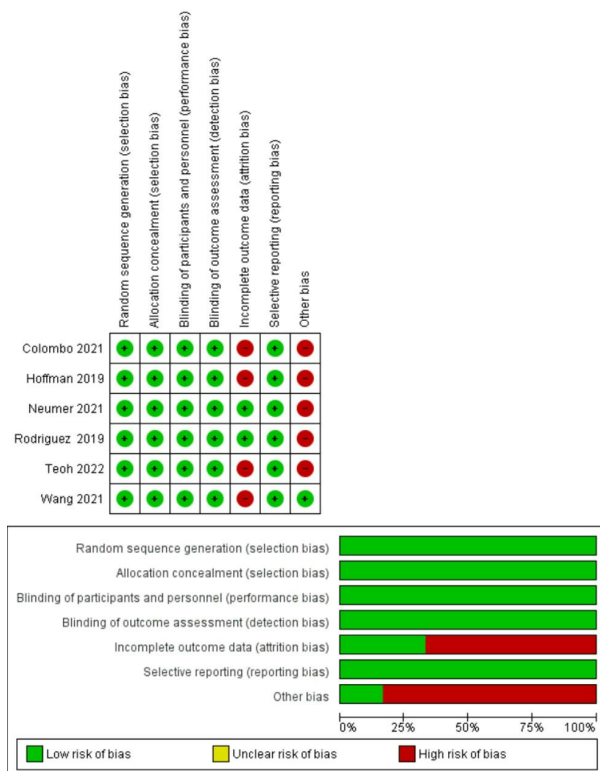


Figure 5. Meta-analysis results on the effect of prebiotics on the gastrointestinal Symptoms: (a) Pre-intervention, (b) Post-intervention

Risk of Bias Assessment

The quality of the articles in the randomized controlled trials and the Version 2 of the Cochrane Risk-of-Bias tool (RoB-2) were used for the randomized trials. The risk of bias was categorized into six domains, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Each domain's risk was rated "low", "high", or "uncertain" based on the predefined criteria of the bias risk tool.

All research has identified an adequate method for randomly assigning participants to treatment groups. Therefore, he rated these studies in this area as having a low risk of nepotism. All studies reported adequate distribution secrecy using sequentially numbered and sealed opaque envelopes and rated them with a low risk of favoritism error. In all studies, the risk of nepotism was low, as both participants and staff were blinded. In all studies, disability between the intervention and control groups was balanced or few enough not to affect the study. For this reason, it was concluded that the risk of attrition was low. Four studies found that the risk of reporting bias was high because anthropometric measurement data were missing or not given at all (9,10,13,14). In addition, in terms of other risks, sponsoring five studies was considered high risk (9-13). For each study included, significant concerns about other possible sources of bias that had not previously been addressed in the above categories were disclosed (Figure 6). The quality of the evidence included in this meta-analysis was assessed using the GRADE approach. Anthropometric measurements, stool characteristics and GI symptoms were the outcomes assessed. The results regarding the outcomes showed low to moderate evidence. The GRADE analysis can be seen in Figure 7.



ROB-2: Risk-of-Bias tool for randomized trials

Figure 6. Risk of bias domains: ROB-2.

DISCUSSION

The purpose of this review and meta-analysis was to summarize the available evidence regarding the infant's growth rate, defecation count and GI outcomes efficacy of probiotic supplementation given to infants compared with controls. The study results are important in terms of showing that probiotic-supported formulas can be used to promote and maintain newborn health, especially when breast milk is not an alternative.

Stool characteristics	10.7	19.5	-0.10	476	Moderate quality	b.High heterogeneity>97.4
Gastrointestinal symptoms	0.09	0.06	-0.01	160	Moderate quality	a.Total population<300
*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio; [other abbreviations, eg. OR, etc.] GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.						

Figure 7. Grade analysis and sum of the findings

The results of the study found that the effect of prebiotics on the growth rates of the babies such as weight gain, head circumference and height was similar between weight gain and height compared with the control group, and the difference between head circumferences was significant. In a text-analysis that included six studies, increases in body weight, head circumference, or length between days 14 and 112 found no positive or negative effect compared with the control groups of the probiotic group. However, this study confirms that normal growth occurs when infants are given a formula containing prebiotics (16). In another study, anthropometric parameters increased in the normal range from visit to visit in the probiotic and control groups and were very similar in the two groups (17). The literature is similar to the study findings.

The results of the study showed that the effect of prebiotics on stool parameters such as stool frequency and stool consistency of infants was significantly different when compared with the control group. Two systematic reviews in China showed that prebiotics reduced the frequency of 24-h stools in infants compared with conventional treatment and that prebiotics were more effective than traditional practices. Our findings supported the claims of the two previous reviews. In a contrary study, it was found that oral probiotic supplementation given to mothers during the perinatal period did not have a significant difference in stool results compared to pesaro (18). A meta-analysis of two studies using *L. reuteri* ATCC 55730 and *L. reuteri* DSM 17938 found a statistically significant increase in the number of fecal evacuations and reported that probiotics may play an important role in

the modulation of intestinal inflammation, which may also contribute (19). Two randomized controlled trials reported that soft stools predominate in infants fed 100% whey partially hydrolyzed formulas (20).

In recent years, scientists have thought that probiotics may be effective for treating GI problems, especially infantile colic (18,20). The results of the study showed that there was no significant difference between the results of vomiting and regurgitation when the effect of probiotics on vomiting and regurgitation outcomes related to GI system symptoms was compared with the control group. Karaahmet et al. (21) reported in their study that infantile colic infants whose mothers were given probiotics had reduced GI symptoms compared with the control group. Baldassarre et al. (18) found that oral probiotic supplementation given to mothers during the perinatal period did not have a significant difference on GI symptoms and stool outcomes compared with placebo. A meta-analysis of three of the six trials in a systematic review that included six randomized controlled trials investigating the efficacy of probiotic supplementation showed a statistically significant reduction in regurgitation compared with placebo in infants receiving *L. reuteri* DSM 17938(22,23) and the original *L. reuteri* ATCC 55730 (24,25) The literature is similar to the study findings.

Limitation

More work is needed, especially in formula-fed babies. Studies evaluating the efficacy of other prebiotics and probiotics are needed, as preliminary results with some of these suggest efficacy. In cases where breastfeeding and breast milk are not an alternative, formula companies have been supporting babies with formulas similar to breast milk content in recent years. However, studies on this subject are very few. In addition, the number of participants included in the sample in the studies was negligible. Of the studies included in the meta-analysis, only two were double-blind and there were no placebo-controlled studies. Also, double-blind and placebo-controlled studies will affect the quality of the included studies.

CONCLUSION

In conclusion, this systematic review and meta-analysis confirmed that prebiotic-enriched formulas are likely to provide benefits for healthy infants. The studies indicate that prebiotic formulas have a positive effect on growth parameters, head circumference, and stool characteristics (consistency, frequency, and density). However, no significant differences were observed in growth or stool frequency. These findings suggest that while prebiotic formulas show potential

for improving infant gastrointestinal health, further research is needed to address the gaps in knowledge in this area.

The healthy growth and development of infants is one of the most crucial factors influencing their lifelong health. The positive effects of prebiotics on the infant digestive system can strengthen their immune system and the development of a healthy microbiota. Therefore, prebiotic-enriched formulas can be considered an important alternative for infants who cannot be breastfed and could be an effective strategy in promoting and safeguarding infant health.



Peer Review Externally peer-reviewed.

Author Conception/Design of Study- D.Ç.T., A.Y.K., F.Ş.B.;

Contributions Data Acquisition- F.Ş.B., A.Y.K.; Data Analysis/ Interpretation- D.Ç.T., A.Y.K., F.Ş.B.; Drafting Manuscript- F.Ş.B., A.Y.K.; Critical Revision of Manuscript- D.Ç.T.; Final Approval and Accountability- D.Ç.T., A.Y.K., F.Ş.B.

Conflict of Interest Authors declared no conflict of interest.

Financial Disclosure Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 03.05.2024
Revision Requested: 02.01.2025
Last Revision Received: 15.01.2025
Accepted: 23.01.2025

Research Article

Open Access

Investigation of the Impact of COVID-19 in Children/ Adolescents with Juvenile Idiopathic Arthritis from a Holistic Perspective: A Controlled Trial



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Abstract

Objective: The study aimed to examine the effect of coronavirus (COVID-19) exposure on the function and quality of life in children/adolescents with Juvenile Idiopathic Arthritis (JIA).

Materials and Methods: 45 children/adolescents diagnosed with JIA (29 female, 16 male) were included. The impact of coronavirus was questioned with the Numerical Analog Scale, disability level with the Childhood Health Assessment Questionnaire (CHAQ), and quality of life with the Pediatric Quality Of Life Inventory 3.0. Module Arthritis (PedsQL). Participants were divided into two groups: JIA with COVID-19 (n=21) and without COVID-19 (n=24).

Results: The mean age of children/adolescents with JIA's mean age was 13.16 ± 3.53 and disease duration was 3.58 ± 2.93 years. There was no difference in impact from coronavirus, quality of life, and disability level between JIA with COVID-19 (46.7%) and without COVID-19 (53.3%)(p>0.05). General health impact from coronavirus had moderate correlation with quality of life-child (r=-0.371) and high correlation with disability level (r=0.511). Psychosocial impact from coronavirus had moderate correlation with quality of life-child (r=-0.493) and quality of life-parent (r=-0.361) and high correlation with disability level (r=0.536). Activity impact from coronavirus had a moderate correlation with quality of life-child (r=-0.371) and a moderate correlation with disability level (r=0.444).

Conclusion: According to our data results, during the pandemic period, children/adolescents with JIA were affected by the coronavirus at the same level whether they had COVID-19 or not, and their quality of life and disability levels did not change. Coronavirus has affected general health and activity, reducing the quality of life and increasing the level of disability. Psychosocially, it reduced the quality of life of both the child/adolescent with JIA and the parents.

Keywords

Juvenile idiopathic arthritis • quality of life • coronavirus

Author Note

The abstract of this study was presented at the Congress of Pediatrik Rehabilitasyonda Güncel Yaklaşımlar held in Denizli-Turkey on 05-06 November 2022.



Citation: Yenil, S., Gür Kabul, E., Başakçı Çalık, B., Kılbaş, G. & Yüksel, S. Investigation of the impact of COVID-19 in children/adolescents with juvenile idiopathic arthritis from a holistic perspective: A controlled trial. Çocuk Dergisi–Journal of Child 2025; 25(1): 10-15. DOI: 10.26650/jchild.2025.1477467

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INTRODUCTION

Coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, was declared a pandemic in March 2020 (1). During this period, education at school was suspended, and measures were taken to prevent the spread of COVID-19, such as banning people under the age of 20 and over the age of 65 from going out, schools giving up face-to-face education and continuing with distance education. These measures caused them to spend more time at home (2). Additionally, making the use of masks mandatory, emphasizing the importance of hand hygiene and the news reflected in the media have caused anxiety and fear in people (2). This has led to psychological effects on various populations, especially vulnerable groups such as children and older adults (3). These restrictions were found to lead to increased sleep disorders in children and adolescents (4) and a decrease in physical activity (5,6), which may also impact their quality of life.

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood. Patients are treated with immunosuppressant agents in most cases, as well as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Due to the use of immunosuppressive medications, they may also have an increased susceptibility to contracting COVID-19. In addition, discontinuing the medication may lead to disease flare-ups and an increased risk of infection. (7). Consequently, the coronavirus outbreak has emerged as a significant source of concern for both families and children. Families with children with JIA have been particularly affected due to evidence of viral transmission in schools or congregate settings by children, who were referred to as “super-spreaders” due to their ability to transmit COVID-19 with remarkable efficiency and serious consequences (8,9). In this regard, a study has shown that children over the age of 13 with rheumatological diseases and their parents are psychologically affected by the coronavirus (10). Confidence in returning to school is low in JIA patients given the risk of COVID-19 (11). Although the disease itself does not directly affect children with JIA, COVID-19 infection may have a significant social impact on the quality of life of these young patients (12).

The study holistically examined the effects of the COVID-19 pandemic in children and adolescents with JIA.

MATERIALS AND METHODS

This study design was cross sectional study. The study was conducted in the pediatric rheumatology clinic and the pediatric rheumatology physiotherapy and rehabilitation unit of a university hospital between January and June 2022. All

patients admitted between these dates were included in the study. Ethical approval of the study was obtained from the local ethics committee at the meeting number of 21 dated 11.30.2021. All individuals were informed verbally and informed consent forms were signed. The patients with JIA were prospectively registered.

Participants

Forty-five children/adolescents diagnosed with JIA (29 female, 16 male) were included in the study. Participants were divided into two groups diagnosed with COVID-19 confirmed by PCR test between 2021 and 2022: JIA with COVID-19 (n=21) and without COVID-19 (n=24).

The inclusion criteria were as follows: JIA diagnosis based on the international league of associations for rheumatology classification (13), age ranging from 8 to 18 years, and willingness to participate. The 8-18 age range was preferred because this study was conducted in the pediatric rheumatology clinic and the pediatric rheumatology physiotherapy and rehabilitation unit of a university hospital, considering the age ranges in the child and parent forms of the Pediatric Quality Of Life Inventory 3.0. Module Arthritis and the fact that children/adolescents with JIA can easily express their own experiences while answering the outcome measures questions.

Exclusion criteria were: presence of any neurological, orthopedic, cardiopulmonary, or other autoimmune disorders, psychiatric conditions impacting cooperation, history of orthopedic surgery within the past year, stable symptoms and medications,

The impact of coronavirus was questioned with the Numerical Analog Scale, disability level with the Childhood Health Assessment Questionnaire (CHAQ), and quality of life with the Pediatric Quality Of Life Inventory 3.0. Module Arthritis (PedsQL). We asked participants to answer the surveys retrospectively, considering the quarantines during the COVID-19 period.

Numerical Analog Scale: The Numerical Analog Scale (NAS) is a scaling tool commonly used to measure subjective emotional or physical states such as pain. NAS provides participants with the ability to assign a numerical value to evaluate a specific condition. This scale is expressed on a numerical scale ranging from 0 to 10, where 0 represents no distress or symptoms and 10 represents the highest level of distress or symptoms. Participants expressed how intense or bothersome they found a particular condition based on their own experiences using a numerical value on this scale. NAS is a reliable measure frequently used in clinical trials or healthcare research (14).



In this study, NAS was used to evaluate the general health, psychosocial, activity, and education impact of coronavirus.

Childhood Health Assessment Questionnaire (CHAQ): CHAQ was developed to assess the functional abilities of children/adolescents. The questionnaire can be applied to all children between the ages of 6 months and 18 years. It consists of 30 questions and 8 subsections. The disability index is a score ranging from 0 to 3, with higher scores indicating greater disability (15).

Pediatric Quality Of Life Inventory 3.0. Module Arthritis (PedsQL): The PedsQL 3.0 Arthritis Module was developed to assess the health-related quality of life in children with rheumatic diseases. The PedsQL 3.0 Arthritis Module includes the subsections "Pain and Hurt" (4 items), "Activities of Daily Living" (5 items), "Treatment" (7 items), "Worry" (3 items), and "Communication" (3 items). It contains 22 items. The PedsQL 3.0 Arthritis Module has child and parent forms for 2-4 years, 5-7 years, 8-12 years and 12-18 years, divided into different age groups. In this study, 8-12 years old and 12-18 years old child and parent forms were used. A high total score on the PedsQL scale means a high quality of life (16).

Statistical Analysis

Power analysis was performed using the G-Power 3.1 program to determine the sample size of the study. In the power analysis based on the HRQoL (KIDSCREEN-10 T-Score) of male children parameter in pre-COVID-19 and within-COVID-19 data of the reference article, it was calculated that 95% confidence and 85% power could be obtained with 38 patients (JIA with COVID-19=19 patients, and JIA without COVID-19=19 patients) ($d = 1.0193$ effect size) (17).

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA) version 26. Demographic data, survey data and parameters obtained by measurement were evaluated with descriptive analysis and given as the average (mean, standard deviation, median, interquartile range, percentage). The Kolmogorov-Smirnov test was employed to assess the distribution of the sample. As the dataset did not conform to a normal distribution, non-parametric statistical methods were used. To compare the impact from coronavirus between the groups, t-test or Mann Whitney-U test was used for the independent groups. Spearman correlation was used to determine the relationship between the impact of coronavirus and the Childhood Health Assessment Questionnaire and the Pediatric Quality Of Life Inventory 3.0. Module Arthritis. The significance level was set as 0.05.

RESULTS

The mean age of the children/adolescents diagnosed with JIA's mean age was 13.16 ± 3.53 and disease duration was 3.58 ± 2.93 years. JIA with COVID-19 was 21 children/adolescents (46.7%) and JIA without COVID-19 was 24 children/adolescents (53.3%). When the participants were divided into two groups: JIA with COVID-19 and without COVID-19, there was a significant difference in age ($p=0.01$). The demographic and disease-related data of children and adolescents with JIA are shown in Table 1.

There was no difference in the impact of coronavirus, quality of life, and disability level between JIA with COVID-19 and without COVID-19 ($p>0.05$) (Table 2). General health impact from coronavirus had negatively moderate correlation with quality of life-child ($r=-0.371$) and positively high correlation with disability level ($r=0.511$). Psychosocial impact from coronavirus had negatively moderate correlation with quality of life-child ($r=-0.493$) and quality of life-parent ($r=-0.361$) and positively high correlation with disability level ($r=0.536$). Activity impact from coronavirus had a negatively moderate correlation with quality of life-child ($r=-0.371$) and a positively moderate correlation with disability level ($r=0.444$) (Table 3).

DISCUSSION

According to our results, during the pandemic, children/adolescents with JIA were found to have similar levels of impact from the coronavirus, regardless of whether they had COVID-19 or not. Their quality of life and disability levels were also found to be similar. In both groups, the coronavirus affected general health and activities, leading to a decrease in the quality of life and an increase in disability levels. Psychosocially, it also reduced the quality of life of parents.

The use of immunosuppressive therapy in chronic rheumatological patients, such as those with JIA, has been a topic of research concerning the risk of increased susceptibility to infection (18,19). The COVID-19 pandemic has led rheumatologists to consider the potential negative impact on the immune system, particularly in relation to a higher risk of COVID-19 and a more severe course of the infection in patients with rheumatic diseases undergoing immunosuppressive therapy (20, 21). Although symptoms and exposure are generally similar to the course of COVID-19 in the healthy pediatric population, it remains a concern for patients and their families (22). Hausmann et al. (2021) demonstrated that during the COVID-19 period, nearly all individuals with rheumatic diseases adopted protective behaviors. Most of them implemented physical distancing or isolation strategies, used masks and gloves, and avoided activities that could



increase the risk of COVID-19. Moreover, the pandemic had serious effects on the education of participants (19). In the

present study, the level of impact of the coronavirus, quality of life, and disability among JIA patients was found to be

Table 1. Demographic and disease-related data of children and adolescents with JIA

	JIA with COVID-19 (n=21) Median (IQR) (Min-Max)	JIA without COVID-19 (n=24) Median (IQR) (Min-Max)	p
Age (years)	15.00 (7.00) (7.00-18.00)	12.00 (6.00) (6.00-16.00)	0.013
Body Mass Index (kg/m²)	17.30 (7.02) (11.87-33.22)	18.61 (7.45) 12.94-27.34	0.865
Disease Duration (years)	2.00 (3.00) (1.00-9.00)	3.50 (5.00) (1.00-11.00)	0.458
	n (%)	n (%)	p
Gender Female Male	13 (61.9) 8 (38.1)	16 (66.7) 8 (33.3)	0.742
Type of JIA			
Oligoarthritis	17 (81)	18 (75)	
RF+ polyarthritis	2 (9.5)	3 (12.5)	
Enthesitis related arthritis	1 (4.8)	3 (12.5)	
Juvenile psoriatic arthritis	1 (4.8)		
Pharmacological Treatment			
No	9 (42.9)	6 (25)	
NSAII	3 (14.3)	5 (20.8)	
Methotrexate	5 (23.8)	3 (12.5)	
Biological therapy	4 (19)	10 (41.7)	

Mann Whitney-U Test, IQR=Interquartile Range, min=minimum, max=maximum.

Table 2. The relationship between impact from coronavirus and quality of life and disability level

	JIA with COVID-19 (n=21) Median (IQR) Min-Max	JIA without COVID-19 (n=24) Median (IQR) Min-Max	p
General health impact from coronavirus	2.60 (4.50) 0.00-6.80	1.80 (2.05) 0.00-6.60	0.255
Psychosocial impact from coronavirus	2.00 (4.85) 0.00-8.75	2.77 (4.10) 0.00-7.75	0.804
Activity impact from coronavirus	2.16 (5.00) 0.00-9.00	2.91 (3.71) 0.67-8.00	0.690
Education impact from coronavirus	3.00 (4.67) 0.00-9.33	3.83 (3.16) 0.00-10.00	0.671
PedsQL-Child	85.20 (31.82) 30.68-100.00	82.35 (18.75) 62.50-98.86	0.285
PedsQL-Parent	89.13 (14.00) 37.00-100.00	83.15 (23.00) 60.00-98.00	0.747
CHAQ	0.37 (0.93) 0.00-3.50	0.12 (0.62) 0.00-2.25	0.310

Mann Whitney-U Test, IQR=Interquartile Range, Min=minimum, Max=maximum, CHAQ= Childhood Health Assessment Questionnaire, PedsQL=Pediatric Quality of Life Inventory 3.0 Arthritis Module.

Table 3. The relationship between impact from coronavirus and quality of life and disability level

	PedsQL-Child		PedsQL-Parent		CHAQ	
	r	p	r	p	r	p
General health impact from coronavirus	-0.371	0.012	-0.290	0.053	0.511	<0.001
Psychosocial impact from coronavirus	-0.493	0.001	-0.361	0.015	0.536	<0.001
Activity impact from coronavirus	-0.328	0.028	-0.234	0.122	0.444	0.002
Education impact from coronavirus	0.029	0.850	-0.063	0.681	0.021	0.893

CHAQ=Childhood Health Assessment Questionnaire, PedsQL=Pediatric Quality of Life Inventory 3.0 Arthritis Module.



the same regardless of whether the patients had contracted COVID-19. This means that COVID-19 did not have a distinct effect on children based on their infection status. Because disease-related restrictions such as curfews, online education in schools, and the use of masks do not change depending on whether the individual is infected or not, these effects on patients and their families may have remained consistent.

In this study, the general health and activity impact of the coronavirus decreased the quality of life and increased disability in children and adolescents. Defects in routine medical checks for children and adolescents during the pandemic, the fear of chronic disease progression, and stress during the quarantine period may have contributed to the decline in quality of life and increased disability by causing general health effects (23). Studies conducted during the pandemic period have shown that the emotional burden increases in individuals with chronic diseases (24). Wilkinson et al. (2021) found that medical treatment was interrupted in 40% of patients with juvenile dermatomyositis and that parents expressed themes of stress, fear, and anxiety throughout the pandemic (24). Similarly, Wahezi et al. (2023) Stated that 30% of patients with juvenile idiopathic myopathy experience interruption of medical care and almost 40% report mental health concerns. In addition, they reported that caregivers mostly discuss the stress they experience regarding protective measures and social isolation, as well as their fears about social isolation (23). In the present study, general health effects such as disruption of children's medical check-ups and increased levels of pain and swelling during the COVID-19 period may have reduced the patients' quality of life and increased disability.

During this period, the quality of life decreased, and the level of disability increased due to the curfew, the closure of gyms and clubs, and the reduction in physical activity. Additionally, as demonstrated in other studies, the increase in screen time among children may have contributed to the decline in physical activity (25). Decreased physical activity levels may also have increased the medical symptoms of these participants and had a greater overall health impact. In addition, the psychosocial impact of coronavirus reduced the quality of life of their families. Duncan et al. (2021) showed that the depression and anxiety scores of patients with rheumatic disease over the age of 13 and their parents were higher than those of the control group, and more than half of the parents believed that their child's rheumatological disease increased the risk of contracting COVID-19 (10). During this period, the closure of schools led to psychosocial effects as well as physical health problems (26). The increase in unemployment and the additional time spent at home with children staying

at home and the decrease in interactions with relatives and friends may have caused problems in interpersonal relationships. In a cohort study, the daily lives of families and children with pediatric rheumatological disease changed during the COVID-19 period (27). The increased psychosocial impact due to both the anxiety caused by the disease and the increasing negative relationships within the family may have contributed to a decrease in the quality of life.

The strength of this study is that, to our knowledge, it is the first controlled study that makes a specific assessment of the situation of children/adolescents with JIA during this pandemic that affects the whole world. It provides information about the perspectives of both children/adolescents and parents. The first limitation is that data on children's sedentary behavior were not recorded. For example, if data on how many hours of television or computer/tablet play were recorded at home, clearer results could be given about how time is spent at home. Second, if data such as fat mass and muscle mass were evaluated before and after a certain period of time, comments could be made about the changes occurring in the body. Another limitation is that we asked participants to respond retrospectively based on the COVID-19 quarantine and lockdown periods. This could have affected individuals' ability to recall accurately, potentially influencing the accuracy of their responses. In addition, disease activity could have been assessed using the Juvenile Arthritis Disease Activity Score (JADAS) to evaluate the outcomes in cases. Disease activity may also have influenced the outcomes.

The findings of this study hold significant relevance for the implementation of preventive measures in the event of future occurrences of natural disasters, pandemics, or similar restrictions. It may guide further research aimed at improving the quality of life and providing psychosocial support for children and their families. In the event of a recurrence of such a period, additional measures, such as remote physical activity interventions facilitated by technology and the ability to conduct medical consultations, could be implemented to minimize the adverse effects on health and quality of life.

CONCLUSIONS

According to our data results, during the pandemic period, children/adolescents with JIA were affected by the coronavirus at the same level whether they had COVID-19 or not. Coronavirus has reduced the quality of life and increased the level of disability in children and adolescents with JIA by affecting their general health and activities. Psychosocially, it reduced the quality of life of both the individual with JIA and the family.





Ethics Committee Approval	Ethical approval of the study was obtained from the Pamukkale University ethics committee at the meeting number of 21 dated 11.30.2021.
Informed Consent	Informed consent was not obtained as it was a retrospective study.
Author Contributions	Conception/Design of Study: EGK, BBC, SY; Data Acquisition: BBC, SY, GK; Data Analysis/ Interpretation: EGK, SY; Drafting Manuscript EGK, SY ; Critical Revision of Manuscript: BBC, SY; Final Approval and Accountability: SY
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 06.09.2024
Revision Requested: 03.12.2024
Last Revision Received: 18.12.2024
Accepted: 27.12.2024

Research Article

Open Access

Investigation of the Awareness of Expectant Mothers About Responsive Care



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Abstract

Objective: This study was conducted to examine the awareness of expectant mothers in the last trimester of pregnancy about responsive care.

Materials and Methods: The study group consisted of 16 expectant mothers who were referred to the Obstetrics and Gynecology Department of a private hospital for NST (Nonstress Test). The data were collected using a demographic information form and a semi-structured interview form. The data were analyzed using the content analysis method by creating categories and subcategories based on similarities. The research data were analyzed in three subcategories: "questions about parental emotion state", "questions about daily life routines", "questions about parent-child relationship/interaction" and "questions about home environment".

Results: Twelve of the expectant mothers stated that their emotional states during the day would directly affect the care they would give to their babies; 16 of them stated that their babies' reactions to the person with whom they perform daily life routines such as sleeping, feeding, changing diapers and playing would differ; 6 of them stated that their babies would express their needs with different crying sounds; 8 of them stated that they did not expect the communication signals for their babies' needs to differ; 15 of them expected their babies to interact during breastfeeding; 6 of them stated that there would be no change in their babies' communication and play in the first year. Expectant mothers stated that they would pay attention to the light, temperature, sound, and number of materials in the room where their babies would sleep and to cleanliness, sound, and crowding in the room where they would feed. While all the expectant mothers thought that the emotional environment in their homes would affect the healthy development of their babies, 7 of them thought that the physical conditions of their homes would not be effective.

Conclusion: The result of the research reflects the expectations and thoughts of the expectant mothers in the study group about the situations that will affect the level of responsive care they will give after birth. It was observed that the knowledge of expectant mothers about responsive caregiving was generally superficial and that they could not answer or gave limited answers to questions that included more details such as causes and effects.

Keywords

Expectant Mothers • Babies • Responsive Care



“ Citation: Budal, K. & Baran, G. Investigation of the awareness of expectant mothers about responsive care. Çocuk Dergisi–Journal of Child 2025; 25(1): 16-25. DOI: 10.26650/jchild.2025.1544575

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INTRODUCTION

From a child development perspective, responsive care for children refers to quality care that is sensitive to the child's needs and supports the child's overall development and well-being (1). A responsive environment and responsive relationships are needed to create a solid foundation for the healthy development of the baby, starting immediately after pregnancy (2). This foundation lays the groundwork for a healthy brain development as well as physical and mental health (3). The main triggers for responsive care are infants' communication cues and how parents interpret these cues (4). All the emotional expressions of the infants, from smiling to crying, attract the attention of adults. This is an evolutionary process that aims to ensure that the care given to infants is under adult control, to recognize any danger, and to ensure the continuation of the species by supporting the infant's well-being in this direction (5).

From the first moments of life, infants display a wide variety of communication cues (6). How quickly, appropriately, and sensitively parents can respond to these cues is considered an important parenting capacity (7). There is a broad scientific consensus on the profound impact of this capacity on child development (8, 9, 10).

Many individual, social and cultural variables affect the caregiving process. For example, perinatal stress, mode of delivery (11), daily sleep duration of the mother and child (12), parental mental health, child temperament, and religious and cultural norms directly affect the caregiving process (13). Therefore, examining the variables affecting the process of responsive caregiving will play an important role in determining the national and global support to be provided to caregivers.

In the literature review and the studies examined, it is seen that environmental conditions, such as the provision or withholding of responsive care, have a lasting effect on the realization of children's innate capacities (14,15). In addition, the World Health Organization, the United Nations Children's Fund, and the World Bank Fund published the "Nurturing Care Framework" in 2018 (16), which is planned in line with the 2015-2030 Sustainable Development Goals (17). The Nurturing Care Framework encompasses parents' responsive caregiving behaviors. Responsive caregiving is a prerequisite for children's healthy development. This is because children need meaningful interactions with the environment and people from the moment they are born. The level of sensitivity of these interactions directly serves the purpose of maximizing the child's developmental potential (18).

The level of awareness on responsive caregiving will affect the quality of care that expectant mothers preparing for parenthood will provide to their infants. In this direction, a way to support child development in the long term is the awareness and knowledge levels of mothers on this issue. For this reason, it is thought that this study will help the literature, mothers and experts in the field to analyze the awareness, thoughts and feelings of mothers about responsive care. This study examines the level of awareness of expectant mothers about responsive caregiving.

MATERIALS AND METHODS

Participants: This research is a descriptive study according to its purpose and a cross-sectional study according to its time, using the phenomenological method, one of the qualitative research types. The study group consisted of 16 expectant mothers who were referred to the Obstetrics and Gynecology Department of a private hospital in Bağcılar district of Istanbul for NST (Nonstress Test). In determining the study group of the research, a deliberate sampling method, one of the non-probability-based sampling methods, was used. The criteria for inclusion of the mothers in the study group were volunteering to participate in the study, being in the last trimester of pregnancy and having her first pregnancy. A method for determining the size of the study group accepted in qualitative research is the saturation of the data (19). When the responses from the mothers started to be repeated, it was considered that data saturation was reached, and the interviews were terminated.

Collection of Research Data: Two midwives working in the NST unit of the hospital were interviewed and from the list of expectant mothers who came for NST, expectant mothers with appropriate gestational week and first pregnancy were identified. First, verbal and then written consent was obtained from the determined expectant mothers. In this process, 20 expectant mothers were reached, and 16 mothers agreed to participate in the study. Expectant mothers were given a participant consent form including the details of the study and were informed that voice recordings would be made because the questions were open-ended. Expectant mothers who agreed to participate and to be audio-recorded signed the consent form. The interviews lasted 25-30 minutes on average. All the interviews were conducted in the section of the hospital where the NST rooms are located. All the rooms in the unit where the mothers were located were single rooms and privacy was protected by separating the front part with a curtain. The audio recordings taken during the interview were transcribed on a computer after the interview.



Data Collection Tools: The research data were collected using the “Demographic Information Form” and “Semi-structured Interview Form” prepared by the researcher. The Demographic Information Form consists of questions prepared to obtain data on the demographic characteristics of the study group (age, education level, working and leave status of expectant mothers and fathers after birth, etc.). The semi-structured interview form was developed by the researcher and the consultant by reviewing the literature, and expert opinion was obtained. Then, the form was finalized with the changes made due to the pilot study.

Statistical Analysis: The MAXQDA program was used to analyze the research data. To protect the confidentiality of the identity information of the expectant mothers who agreed to participate in the study, codes between P1-P16 were assigned. The codes were created according to the order of data collection. In the next stage, all the data obtained were read and their contents were analyzed, and categories and subcategories were created. The categories and subcategories prepared by the researcher were examined and compared by three independent Child Development Experts as recommended by Braun and Clarke (2006) to ensure

Table 1. Opinions on caregiving behaviors

Categories	Subcategories	Frequency	Participant Code
Effects of their own emotional state on the care they will give to their babies			
Affects	The mother's emotional state is reflected in the child.	7	P2, P3, P5, P6, P9, P11, P13
	It affects the quality of caregiving.	4	P1, P4, P12, P16
	It affects the baby's development.	2	P8, P13
Does not affect	-	4	P7, P10, P14, P15
The effects on the child of the regularity of the baby's activities of daily living			
It's important, I think it will impact my baby's development	Effective in establishing a sleep routine (training).	5	P1, P5, P8, P10, P15
	It is effective in establishing a sleep and nutrition routine.	6	P2, P3, P4, P6, P7, P14
	It has a positive impact on your development.	6	P4, P5, P7, P8, P14, P15
	It is effective in helping the baby learn (routines, the concept of time, etc.).	3	P1, P6, P12,
	It is effective in maintaining routines in later life.	1	P13
It doesn't matter, I don't think it will affect my baby's development	What is important is that needs are met, not that they are regularized.	1	P11
Sleep is important, others are not	The sleep routine impacts behavioral, cognitive, and emotional development.	1	P9
	It has a positive impact on the child's developmental level and self-expression skills.	1	P16
The different signals that babies give about their needs			
Differentiates	The sound of crying is different.	6	P4, P6, P9, P10, P14, P16
	There is a change in behavior.	1	P8
	It opens its mouth when hungry.	2	P10, P14
	His facial expression changed.	1	P16
	I don't know how it will be different.	1	P3
It does not differentiate as a baby; it differentiates as it grows	When they are small, they only cry.		
	As it grows older, it shows its needs physically.	3	P5, P7, P15
Does not differentiate I do not know	Only cries.	3	P1, P12, P13
	-	2	P2, P11

the validity and reliability of the qualitative data. In this way, the consistency of the categories and subcategories was ensured (20).

Ethical Aspect of the Study: The ethics committee approval of the study was obtained from the Istanbul Medipol University Social Sciences Scientific Research Ethics Committee with the date 22.05.2023 and number E-43037191-604.01.01.01-22172. Following the approval of the ethics committee, written approval was obtained from the chief physician of the hospital to conduct the study.

RESULTS

The demographic characteristics of the expectant mothers who participated in the study are as follows. The mean age of the mothers participating in the study was 28.88 ± 2.94 and the mean age of the prospective fathers was 30.1 ± 3.4 . One of the mothers was a high school graduate, 14 were undergraduates and 1 was a postgraduate graduate, while one of the fathers was a primary school graduate, 6 were high school graduates and 9 were undergraduates. The perceived income level of 1 expectant mother was low, 8 were medium and 7 were good. All of the expectant mothers were married, and 13 of them had been married for 0-2 years, 2 for 3-4 years, and 1 for 4-5 years. Information on the opinions of expectant mothers about the effects of their emotional states on the care they will give to their babies, the effects of the regularity of the baby's daily life activities on the child, and the different signals they give about their babies' needs are shown in Table-1.

When the expectant mothers were asked whether their emotional state would affect the care they would give to their babies, 12 expectant mothers stated that it would (Table 1). They stated that their emotional states such as happiness, sadness and tension could be reflected on their babies and that these emotional states could affect the quality of care they would give to their babies or that they could be negatively affected in areas such as emotional development and language development. Examples of the answers given by the mothers are as follows:

P3: *"...I think that the happier I am, the more willingly and willingly I take care of my baby, the happier and more peaceful my baby will be."*

P16: *"...So in an environment where I'm unhappy, I don't think I can respond to my baby in a very productive way."*

P13: *"I mean, if you are negative all the time, I think the baby will also be negative and cry....If there is a negative situation, it affects the child, it affects his development, it affects his speech, it affects his walking."*

The 4 expectant mothers who thought that their emotional states would not affect the care they would give to their babies stated that they would be sure that the care they would give to their babies would always be the same in all emotional conditions (Table 1). An example of the answers given by the expectant mothers who thought in this way is as follows:

P10: *"I mean, I don't think it will affect me. I must take care of my child no matter how I am, I don't think it will affect me."*

When the expectant mothers were asked about the effects of regularity in daily life activities such as sleep, nutrition and play on the child, 13 expectant mothers stated that it would contribute to the healthy development of the baby and would be especially effective in terms of establishing a sleep and nutrition routine (Table 1). Examples of the answers given by the mothers are as follows:

P10: *"It will definitely have an effect..... I am already researching sleep training and play training.... I think I will be consistent about sleep training, sleep training and regular sleep will positively affect your life."*

P14: *"Of course I think it will have an impact..... it's really a problem for children when the order is disturbed..... mothers have to sacrifice some things..... When sleep is disturbed, it affects development and nutrition.."*

The expectant mother who thought that this would not be effective expressed her opinion as follows:

P11: *"I mean, if the baby's daytime sleep is 2 hours a day, yes, 2 hours of sleep is done, but I don't think it should always be at the same time."*

When the expectant mothers were asked whether the symptoms of wanting their babies' needs, such as sleepiness, hunger and changing diapers, to be met would differ, 8 expectant mothers stated that they would (Table 1). Among the expectant mothers who thought that there would be a difference, 6 of them stated that there might be a difference in the crying sound of their babies in line with the information they obtained from the environment. The other expectant mothers thought that they could show their needs behaviorally, such as opening their mouths when they were hungry and changing their facial expressions. For example, one of the expectant mothers expressed her opinion as follows:

P14: *"Forty days after birth, there is a difference, there is a way of crying.....with the mouth, for example, some babies do a lot of things, they are searched for, they open their mouth slurping like this, some open their mouth when they are hungry."*

Table 2. Opinions about the home environment

Categories	Subcategories	Frequency	Participant Code
Features of the baby's sleeping room			
Appropriate temperature	-	7	P1, P4, P6, P10, P11, P13, P15
Appropriate humidity	-	3	P1, P4, P15
Appropriate light	-	11	P1, P2, P4, P6, P7, P8, P9, P10, P14, P15, P16
Well ventilated/spacious	-	6	P3, P7, P9, P11, P12, P15
Free of excess stimuli	-	7	P1, P5, P8, P9, P13, P14, P15
Silent/quiet	-	9	P2, P3, P5, P6, P7, P8, P10, P14, P15
Clean	-	5	P2, P3, P7, P11, P13
Safe	-	1	P2
Color of the room	-	3	P5, P7, P12
The effects of the characteristics of the room where the baby will sleep on the baby			
Impacts	Easy/difficult transition to sleep	6	P1, P4, P6, P9, P15, P16
	Increase/decrease in the sleep duration	7	P3, P5, P8, P9, P10, P14, P15
	Establishment of sleep patterns	4	P2, P10, P15, P16
	Increased/decreased sleep quality	4	P4, P7, P8, P14
	Nightmares	1	P14
I don't know	-	2	P11, P12
Effects of the physical conditions of the home environment on child development			
The physical environment has an impact on a child's healthy development.	It should support independence/individualization.	2	P4, P16
	It affects the level of taking responsibility.	2	P8, P14
	Positive/negative effects.	1	P12
	It makes him/her feel he/she belongs.	1	P13
	It affects the development of motor skills such as crawling and walking.	1	P16
	I don't know.	3	P3, P5, and P6
The physical environment does not influence a child's healthy development.	Security measures must be in place.	1	P1
	-	5	P2, P7, P10, P11, P15
I don't know.	-	1	P9
Effects of emotional conditions in the home environment on child development			
The emotional environment has an impact on a child's healthy development.	Positive/negative role modeling	1	P1
	Positive/negative impact on emotional development/psychology	14	P2, P3, P5, P6, P7, P8, P9, P10, P11, P12, P13, P14, P15, P16
	Healthy realization of daily life routines	1	P4
	The child is autonomous	1	P11

3 of the expectant mothers stated that they did not expect any changes during infancy and that they would be able to express this as they grew older; the only communication signal of babies is crying (Table 1). For example:

P15: "Normally, when a newborn is born, he always reacts by crying when he is hungry and when he gets his diaper, so....but it will differ in every period in terms of age."

P13: "I don't think it will make a difference, she will cry, I know that."

The mothers who answered “I don't know” mentioned that they had no idea whether it would change or not since it would be their first baby. For example:

P2: *"I don't know, I assume he yawns when he gets sleepy. I don't know, I don't have any children."*

Information on the views of expectant mothers about the characteristics of the room where their babies sleep, the effect of these characteristics on their babies' sleep, and the effects of the physical and emotional conditions of their homes on child development is shown in Table-2.

As shown in Table 2, expectant mothers stated the features they would pay attention to in the room where their babies would sleep as follows:

P4: *"I like to sleep in the dark and I know that it is healthy. We plan to put the children to sleep in an environment that is usually dark or very dark. We are already trying to organize a room accordingly. Apart from that, I learned that there are details such as the temperature balance and the humidity balance. We tried to adjust them."*

P11: *"I just ensure that it is clean, airy, warm. She will want to be with me anyway. Then, when he has his own space, I try to create a place where he can play more, where he can hang out more freely."*

P7: *"Clean, spacious, bright, I think the house I like will be bright. Furthermore, a little calmness."*

Expectant mothers were asked whether the characteristics of the room where their babies slept would affect their babies' sleep and if so, how. While 14 expectant mothers thought that it would affect, 2 expectant mothers stated that they did not know whether it would affect or not (Table 2). Expectant mothers who thought that it would affect their babies' sleep stated that the room features would make it easier or more difficult for their babies to transition to sleep, and that variables such as heat, light and sound during sleep would decrease or increase sleep time or affect sleep quality. For example:

P9: *"As I said, even if there is a sound at the moment when the child is about to fall asleep, even if it comes from outside, when the child wakes up and sees a toy around, his sleep may be disturbed, and he may want it. He may want to play with it, then his sleep is disrupted, and his sleep time is shortened."*

The answer of one of the expectant mothers who answered “I don't know” is as follows:

P11: *"I don't know whether it will affect it or not. I mean, a noisy environment can affect it, but I don't know if the room itself affects it."*

When asked about the effect of the physical conditions of the home environment on child development, 9 expectant mothers stated that the physical environment may have an effect on child development, 6 expectant mothers stated that it would not have an effect, and 1 expectant mother stated that she did not know whether it would have an effect or not. The reasons for thinking that it would or would not have an effect are given in the subcategories in Table 2. Examples of the responses of expectant mothers who thought that it would have an effect are as follows:

P16: *"Of course, having an area where he can crawl and walk, the house is cool, in conditions like Istanbul..."*

P4: *"Having a room of their own will be important for their individualization."*

5 expectant mothers stated that the physical environment would not affect child development, while 1 expectant mother stated that she know nothing about the subject. An example of the answers of the expectant mothers who think that it will not have any effect is as follows:

P1: *"I don't think the physical environment will affect much, except in terms of danger."*

All the expectant mothers think that emotional conditions in the home environment will impact child development. Fourteen of the 14 expectant mothers who participated in the study stated that emotional conditions would impact the psychological well-being and emotional development of their children.

P7: *"I mean, I don't think that a child with a high level of shouting in a house where there is a constant argument will have a superb psychology and grow up."*

P8: *"The communication between my spouse and me or the creation of happy moments at home will affect his/her development as it will affect his/her psychology."*

DISCUSSION

In this study, which aimed to examine the awareness of expectant mothers about responsive caregiving, most of the mothers thought that their emotional states would affect the care they would give to their babies, while very few thought that it would not (Table 1). Studies have shown that the emotional states of mothers have a significant effect on the development of their babies (21). For example, Punamäki et al. reported that the mother-infant attachment of expectant mothers in a war environment predicted the healthy development of the infant and maternal mental health (22). In another study, Behrendt et al. found that emotional regulation difficulties and depressive symptoms in mothers predicted less responsive care behaviors through

weak attachment patterns (23). Similarly, Walker et al. found that the maternal anxiety level affected the mental health of their children in early childhood (24). When the literature is reviewed, it is seen that there are many studies showing that the caregiving behaviors provided by the mother, the mother-child relationship and the quality of the mother-child interaction are generally affected by the emotional state of the mother (21,25,26,27). It is thought that this effect is not limited to a short period of time after birth but may lead to long-term consequences and may affect the mental health and emotional problems of the child in later childhood (28).

Most of the expectant mothers who participated in our study thought that meeting their babies' needs such as sleep, feeding and play at the same times of the day and regularly would be effective on their babies' development. When asked what kind of effect it would have on their babies' development, they gave superficial answers such as that it would be effective in establishing a routine and have a positive effect (Table 1). When the literature on the effect of regularity of caregiving behaviors on infants is examined, it is seen that establishing daily routines is extremely important in terms of predictability and safety (29). Predictable caregiving behavior in infancy positively supports children's cognitive and emotional development in the long term (30). The fact that the caregiver is sensitive to the needs of the infant and provides regular care in line with these needs ensures predictability and thus makes the infant feel safe (31). In addition, it is thought that regular and unpredictable care may lead to the activation of stress response systems in the infant and cause early maturation of the corticolimbic system (32). The corticolimbic system, which consists of the prefrontal cortex, amygdala, and hippocampus, is responsible for a wide range of behavioral and cognitive functions, including motor programming and control, decision-making, mnemonic function, and emotional regulation (33). Research on the effects of premature maturation of the corticolimbic system is ongoing, but it is thought to have long-term negative consequences for brain development and emotional development (34).

Another issue examined within the framework of responsive care is the communication signals of infants. Infants communicate their physiological needs such as hunger, diaper change, and gas through various communication signals (35). Infants can convey these signals to their caregivers in various ways, including rapid and transient facial expressions, gestures, bodily movements, and vocalizations (36,37). Although the exact meaning of these signals is not known, studies have reached a consensus on infant signals in some situations such as basic hunger, satiety and liking

(37,38). Durak and Bayındır (2021) conducted a study in which they classified infants' cries according to their needs using machine learning. Because of the study, the baby's crying (hungry, sleepy, colic, painful, etc.) was classified with a 93% success rate (38). It is thought to be essential for mothers who have difficulty in understanding social communication and communication cues to get help from technology to make the care they give to their babies more sensitive.

Most of the expectant mothers who participated in our study emphasized the need for appropriate lighting in the environment where their babies would sleep. Appropriate lighting meant providing a completely dark environment for some mothers, while for others it meant providing a dim environment. Expectant mothers thought that room characteristics would affect their babies' sleep duration and transition to sleep (Table 2). In the literature, the provision of various behavioral and environmental factors that contribute to healthy and quality sleep is referred to as "sleep hygiene". Creating a sleep hygiene environment for infants is essential for their well-being and development (39). It is said that the environment in which the baby will sleep should have various characteristics to ensure sleep hygiene. The mattress on which the baby will sleep should be cotton and not too soft. It is also an important factor that the clothes the baby will wear while sleeping should be cotton, should not restrict his/her movements and should not be too thick or thin according to the room temperature. In line with the statements frequently expressed by the expectant mothers who participated in our study, studies show that light is a dominant environmental cue affecting the sleep-wake cycle. Prayag et al. (2019) conducted a review study discussing how specific characteristics of light, such as intensity, duration, timing, pattern, and wavelengths, affect sleep and wakefulness in humans through their effects on alertness or circadian rhythm. They concluded that exposure to inadequate light, such as too much blue-enriched light during circadian rhythm times, such as just before bedtime, can severely alter sleep physiology and lead to sleep disturbances in cases of chronic exposure (39). In summary, creating an optimal sleep environment for infants requires consideration of various factors such as light, temperature, and sleep quality.

While some of the expectant mothers who participated in our study thought that the physical conditions of the home environment would be effective on child development, another part of the expectant mothers thought that it would not be effective (Table 2). In the literature, many studies have shown that the quality of the home environment is a crucial factor in supporting optimal child development (40,41,42).

In their study, Kuhn et al. (2021) aimed to examine the relationship between the home environment and early child development in underdeveloped rural areas by collecting data from 445 children living in rural areas in the Guizhou province of China. They used a demographic information form, the Home Environment Observation List (HOME), and the Bayley-III Developmental Screening Inventory to collect data. According to the results of the study, a significant and positive relationship was found between the presence of learning materials at home, sensitivity of caregivers and organization subscales and early development of children (43). In parallel with this study, most of the expectant mothers who participated in our study stated that the physical conditions of the home environment would be effective on child development. However, when the expectant mothers were asked what kind of effect this would have on development, they gave non-detailed answers.

All the expectant mothers who participated in our study thought that the emotional conditions of the home environment would impact the development of their children. The majority of them stated that this effect would affect the psychology of their children (Table 2). In parallel with the responses of the expectant mothers, the emotional atmosphere of the home environment has an impact on the child's developmental areas such as cognitive, psychomotor and sociol-emotional. There are many factors affecting this emotional atmosphere. Positive parenting practices (44), emotional intelligence of parents (45), temperament characteristics and harmony between spouses are some of these factors (46). For example, Miller et al. (2016) conducted a study to test whether biological stress hormones influence the relationship between positive and negative home environment characteristics (routines; chaos) and emotion regulation. One of the aims of the study was to examine the relationship between home environment characteristics (routines; chaos) and emotion regulation. The study was conducted with 380 low-income families and their children. According to the results of the study, there is a negative and significant relationship between chaos at home and the emotional regulation skills of children (47).

It was observed that the information obtained from the expectant mothers participating in the study from various information sources was compatible with scientific studies at the basic level. However, it was observed that they generally had difficulty in the questions they were asked to elaborate. It is thought that the reason for this is that the mothers received short information from the sources where they obtained information about child development and responsive caregiving, but they did not have sufficient

information on issues such as the causes, types and factors affecting this information.

Data for the current study were collected from a single hospital. The inability to reach a wider socioeconomic and sociocultural population is a limitation of the scope of the study. Due to the deliberate sampling and descriptive nature of the study group, it does not represent larger groups. The generalizability of the study can be increased by designing it relationally with larger groups. Another limitation of the study is the assumption that the expectant mothers in the study group answered the questions sincerely.

CONCLUSION

The results of this study, which was conducted to examine the awareness of expectant mothers about responsive care, showed that expectant mothers did not have sufficient knowledge about the process of responsive caregiving. While answering the questions, the expectant mothers frequently gave examples from other babies and their mothers that they observed around them. This situation suggested that the expectant mothers did not obtain their knowledge from formal sources but through observation. Expectant mothers' views on whether various factors would affect the development of their babies or whether there would be differences in their babies during the process of giving sensitive care are in parallel with the information in the literature. However, it is thought that the answers to more in-depth questions such as what these effects or differences are caused by, what kind of effects they may have or how they may result are at a superficial level.



Ethics Committee Approval	The ethics committee approval of the study was obtained from the Istanbul Medipol University Social Sciences Scientific Research Ethics Committee with the date 22.05.2023 and number E-43037191-604.01.01.01-22172. Following the approval of the ethics committee, written approval was obtained from the chief physician of the hospital to conduct the study.
Informed Consent	Written consent was obtained from the participants.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- K.B., G.B.; Data Acquisition- K.B.; Data Analysis/Interpretation- K.B., G.B.; Drafting Manuscript- K.B.; Critical Revision of Manuscript- G.B.; Final Approval and Accountability- K.B., G.B.
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 20.09.2024
Revision Requested: 11.02.2025
Last Revision Received: 09.03.2025
Accepted: 17.03.2025

Research Article

Open Access

Evaluation of Quality of Life in Children With Allergic Rhinitis



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Abstract

Allergic rhinitis (AR), caused by IgE-mediated inflammation of the nasal mucosa due to allergens, affects 20–40% of Europe and the U.S. population, with varying prevalence in other regions. The study investigates the impact of allergic rhinitis (AR) on the quality of life (QOL) in school-aged children. It evaluates the effectiveness of the Pediatric Rhinitis Quality of Life Questionnaire (PRQLQ) in assessing disease severity and treatment outcomes. It uses the ARIA classification to categorize rhinitis severity. By analyzing QOL scores before and after treatment, the study assesses how well the PRQLQ reflects changes in disease severity and improves understanding of AR's impact on children's daily lives. The study used a prospective, longitudinal design to evaluate the impact of allergic rhinitis on children's QOL before and after treatment. It included 120 children aged between 6–12 years, diagnosed with allergic rhinitis, and assessed using the Pediatric Rhinitis Quality of Life Questionnaire (PRQLQ) at the start and six weeks after treatment. Data were analyzed for changes in QOL scores across different rhinitis severity groups (via ARIA classification), considering sociodemographic factors and treatment effects. Results showed significant improvements in QOL scores post-treatment across all rhinitis groups. The PRQLQ scores, including subscales for nasal symptoms, eye symptoms, practical issues, and activity limitations, decreased significantly after treatment, indicating improved QOL. The study found that more severe rhinitis led to lower QOL before treatment, but significant improvements were noted in all groups after treatment. The PRQLQ effectively measured these changes and highlighted the substantial impact of allergic rhinitis on school-aged children's daily lives, underscoring the importance of effective treatment in enhancing their quality of life.

Keywords

Child health • quality of life • allergic rhinitis • treatment



“ Citation: Erdemir Kula, M. & Nursoy, M. A. Evaluation of Quality of Life in Children With Allergic Rhinitis. Çocuk Dergisi–Journal of Child 2025; 25(1): 26–32. DOI: 10.26650/jchild.2025.1553779

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INTRODUCTION

Allergic rhinitis (AR) is a symptomatic condition resulting from IgE-mediated inflammation of the nasal mucosa membrane upon exposure to allergens (1). Symptoms such as postnasal drip, throat clearing and sniffing, palatal click, itching, sneezing, and nasal congestion occur due to IgE-mediated mast cell degranulation (2). AR is one of the most common chronic diseases in children worldwide. Prevalence increases with age: 5% at age 3; 8.5% at ages 6–7 and 14.6% at ages 13–14 (3). Although significant geographic variations exist, studies have shown that the prevalence of self-reported allergic rhinitis symptoms in children is 18,12% while physician-diagnosed AR is 10,5% (3, 4). In our country, studies indicate an increasing trend in the AR prevalence. A recent study in the Central Black Sea region found that 3.1% of children had AR, showing a significant increase compared to 20 years ago (5). In Konya, the prevalence of AR was found to be 43.2%, higher than in previous years (6). Recent research highlights that AR is strongly associated with asthma (10–40% of AR patients have asthma), sleep disturbances, atopic dermatitis, and sinusitis (7, 8).

The Allergic Rhinitis and Its Impact on Asthma (ARIA) classification is a global guideline developed in collaboration with the World Health Organization (WHO) to standardize the diagnosis, classification, and treatment of allergic rhinitis (AR). The ARIA classification divides allergic rhinitis (AR) at frequency (intermittent or persistent) and severity (mild or moderate-severe). Intermittent AR occurs for less than four days per week or four consecutive weeks, whereas persistent AR lasts longer. Mild AR has no major impact on daily life despite moderate-severe AR causing severe symptoms such as significant nasal congestion or discomfort, sleep disturbances, and impairment in daily activities, school, or work performance (7).

The diagnosis relies on a detailed history, physical examination, and allergen-specific tests. Skin prick tests (SPT) and serum-specific immunoglobulin E measurements are fundamental diagnostic methods for identifying allergens. Serum total IgE testing is an alternative, especially in cases where SPT is not possible (such as a child has dermatographism). Nasal eosinophilia and Basophil Activation Tests (BAT) have potential use in pediatric AR diagnosis, but data is still limited. Although treatment typically begins with environmental measures to avoid allergens, pharmacological agents such as intranasal corticosteroids (INCS) are often preferred for controlling moderate-severe symptoms as the first-line. Other treatment options include nasal irrigation, intranasal antihistamines, oral H1 antihistamines, intranasal anticholinergics, nasal decongestants, and leukotriene

receptor antagonists (only in combination with INCS when needed), and allergen-specific immunotherapy (3, 8).

As allergic rhinitis was not life-threatening, research showed that many parents did not seek medical treatment or over-the-counter remedies. However, this condition could significantly affect children's cognitive and psychomotor functions, learning abilities, sleep, and participation in social activities, impairing their quality of life (9). Both ARIA and ICAR (International Consensus Statement on Allergy and Rhinology) emphasize the need for systematic QoL assessment in children with AR to monitor treatment effectiveness, guide management decisions, and improve patient-centered care (7, 8). To evaluate the quality of life in children with allergic rhinitis, Juniper et al. developed the Pediatric Rhinitis Quality of Life Questionnaire (PRQLQ) in 1998, which was translated into Turkish by Hasan Yüksel et al. in 2009 (10, 11). In patients with both asthma and allergic rhinitis, general quality of life scales (e.g., PedsQL) or specific scales for both (such as CARATKids for children and RHINASTHMA-Adolescents for adolescents) could be used (12–14). Ecological momentary assessments (EMA) are a new method that depends on repeated measurements of daily symptoms to better reflect the severity of disease and QOL better (15). This study aimed to investigate the impact of allergic rhinitis on the quality of life of school-aged children before and after treatment and to assess the applicability of quality-of-life scales in determining disease severity and monitoring treatment.

METHODS

Our study was designed as a prospective, longitudinal, pre-post type. Sample size determination was performed using the G-power 3.1.9.2 software. The analysis indicated that 120 participants would be required with an effect size of 0.5 and 80% power. Ethical approval was obtained from the Bezmialem Vakıf University Clinical Research Ethics Committee. Written and verbal consent was obtained from all parents and verbal consent from the children.

The study was conducted with 120 volunteer children and their parents who were diagnosed with allergic rhinitis and met the inclusion criteria (see Table 1: Inclusion and Exclusion Criteria) at Bezmialem Vakıf University Faculty of Medicine Pediatric Allergy Clinic between December 2015 and January 2016. Patients were classified into four groups based on the ARIA classification according to symptom frequency and severity (7). The routine treatments (INCS, oral antihistaminic (OAH), INCS and OAH and LTRA) were started due to disease severity, as recommended in the ARIA guidelines.



Table 1. Inclusion and exclusion criteria

Inclusion Criteria	1. Providing informed consent to participate in the study 2. Aged 6 to 12 years. 3. Clinical symptoms consistent with allergic rhinitis with at least one positive skin prick test result for an allergen. 4. Newly diagnosed or previously diagnosed but untreated for at least 2 months. 5. Patients who were at the beginning of routine treatment (INCS, OAH and or LTRA)
Exclusion Criteria	1. Presence of any chronic disease other than mild persistent asthma or mild intermittent asthma 2. Patients receiving specific immunotherapy and any treatments other than INCS, OAH, or LTRAs.

Descriptive data about the patients, including parents' socioeconomic status (age, occupation, education level, monthly income), number of siblings, household size, type of home heating, smoking exposure, presence of pets, and family history of atopy, were collected through a face-to-face questionnaire administered by the responsible researcher. The socioeconomic status of the families was determined by calculating the weighted average of the scores from the patient information form, with scores below 1 standard deviation considered low, between 1 and +1 standard deviation considered medium, and above +1 standard deviation considered high (16).

The skin prick test results, serum total IgE levels, and serum eosinophil percentages of each participant were retrieved from patient records at the Pediatric Allergy Outpatient Clinic, Bezmialem Faculty of Medicine. Skin prick tests had been performed on the forearm using major allergens, including grass, tree, weed pollens, mold, cat, dog, cockroach, and house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*) (Allergopharma®, Germany). Egg yolk, egg white, and chicken meat had also been tested with skin prick tests in some patients who were suspected of having food allergies (Allergopharma®, Germany). Serum total IgE levels were measured in all children using the chemiluminescent enzyme immunoassay method with the Immulite 2000 analyzer (DPC, Los Angeles, CA).

The PRQLQ was used to assess the QOL scores of the participants before and after the routine treatment. The questionnaire consists of 23 questions about the patient's condition over the past week. Four questions address nasal symptoms, four address eye symptoms, five address practical issues, six address other problems, and four address activity limitations (11). PRQLQ responses range from 0 to 6, with higher total scores indicating worse QOL. The PRQLQ was

administered to children face-to-face by the researcher at the start of treatment and by phone at the 6th week.

Categorical data are presented as n and %, while continuous data are presented as mean $\pm$ standard deviation or median (range) depending on the distribution characteristics. Continuous data distributions were tested using the Kolmogorov-Smirnov test. Comparisons of non-parametric data were made using the Mann-Whitney U test, Wilcoxon signed-rank test, and Kruskal-Wallis test, while parametric data were compared using the dependent samples t-test, independent samples t-test, and one-way ANOVA. Post-hoc Tukey tests were performed for significant findings in multiple comparisons. Analyses were conducted using SPSS 20. Categorical data were evaluated using the chi-square test, and a *p* value of 0.05 was accepted as statistically significant.

RESULTS

The study was completed with 120 patients (45.8% female, 54.2% male), with a median age of 9 years (min-max: 6-12 years). The sociodemographic and clinical characteristics are shown in (Table 2). According to the skin prick test results, 83.9% of the patients were sensitive to dust mite allergens, while 15.9% were sensitive to multiple allergens. The multi-allergen group had sensitivities to dust mites and other allergens such as pollen (including cereal and grass mix), mold, cat dander, dog dander, egg white, egg yolk, and chicken meat. The rate of children with multi-allergen sensitization was similar in the mild (12/60; 20%) and moderate/severe AR (9/60; 15%) groups. The children with allergic rhinitis (AR) who had comorbid asthma (15/60; 25%) compared with those with AR only (6/60; 10%) had more frequent multi-allergen sensitizations ($p = 0.031$, χ^2 test). The median serum total IgE was 176,42 (min-max: 1,00-3000,00) IU/mL in children. There was no statistically significant difference between the serum total IgE levels of the mild-intermittent AR, mild persistent AR, moderate/severe intermittent AR or moderate/severe persistent AR groups.

As participants were classified into four groups via the ARIA classification, each group had 30 children. The groups were intermittent mild rhinitis, intermittent moderate-severe rhinitis, persistent mild rhinitis, and persistent moderate-severe rhinitis, totaling 120 patients. The PRQLQ was applied and repeated after six weeks of treatment. Significant reductions were observed in both the total and subscale scores after treatment (Figure 1: Pre-treatment and Post-treatment Values of Subscale Scores). The total scale scores by rhinitis classification showed that patients with intermittent mild rhinitis had lower scores than those in other rhinitis groups both before and after treatment. Significant reductions

Table 2. Sociodemographic and clinical characteristics of the children

Sociodemographic characteristics	n=120	%
Gender		
Female	55	45.8
Male	65	54.2
Age (years)¹	9.0	(6.0-12.0)
Socioeconomic status		
Low	25	20.8
Medium	81	67.5
High	14	11.7
Family history of atopy		
None	54	45.0
Present	66	55.0
Exposure to smoking		
None	47	39.2
Present	73	60.8
Presence of pets		
None	103	85.8
Present	17	14.2
Diagnosis		
Mild intermittent rhinitis (MIR)		
• MIR with asthma (n=15)	30	25
Moderate-severe intermittent rhinitis (MSIR)		
• MSIR with asthma (n=17)	30	25
Mild persistent rhinitis (MPR)		
• MPR with asthma (n=15)	30	25
Moderate-severe persistent rhinitis (MSPR)		
• MSPR with asthma (n=13)	30	25
Skin prick test (SPT)		
Sensitive to dust mite allergens only (D. Pteronyssinus (d1) and D. Farinae (d2))	99	83.9
Sensitive to multiple allergens		
• Aero-allergens (n=19)		
d1 and d2 and pollen mix and cereal grains (n=8)		
d1 and d2 and cat dander with/without dog dander (n=6)		
d1 and d2 and cat dander and pollen mix with/without cereal grains, tree and mold 1 (n=2)		
(d1 and d2 and mold1, pollen mix, cereal/grains (n=1)		
d2 and mold 1 and mold 2 (n=1)		
Cat dander and dog dander (n=1)		
• aero- and food allergens		
(d2 and mold 1 and mold 2 and chicken meat) (n=1)		
• food allergens		
(egg white and egg yolk, and chicken meat (n=1))	21	16.1
Serum total IgE¹ (IU/mL)	176,40	(1.0-3000)
Serum eosinophils %		
<4%	47	39.2
≥4%	73	60.8

Median, minimum, and maximum values are shown for the continuous variables.

in the total scale scores were observed in all rhinitis groups after treatment (Figure 2).

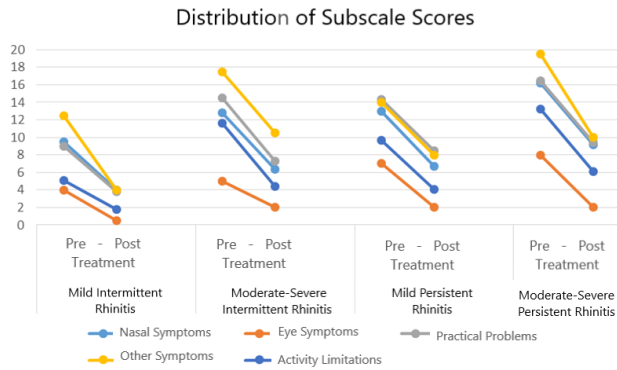


Figure 1. Pre- and post-treatment Values of Subscale Scores ($p < 0.001$ for all).

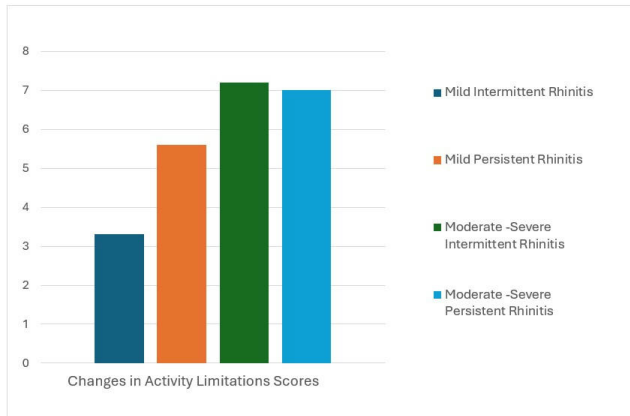


Figure 2. Changes in Activity Limitations Scores Following Rhinitis Treatment ($p=0.001$).

Table 3. Distribution of Changes in Scale Scores According to Rhinitis Diagnosis Categories and Their Association with Asthma

Condition	Mild Rhinitis	Mild Rhinitis + Asthma	Moderate-Severe Rhinitis	Moderate-Severe Rhinitis + Asthma	p value ¹
N-difference	6.3 (4.1)	5.5 (3.6)	6.9 (3.7)	6.5 (5.2)	0.592
E-difference²	3.0 (-4.0 to 12.0)	3.0 (-2.0 to 14.0)	4.0 (-2.0 to 17.0)	3.5 (-4.0 to 11.0)	0.782
P-difference	5.7 (3.8)	5.4 (3.9)	7.1 (4.3)	7.1 (5.2)	0.253
O-difference²	5.5 (-4.0 to 18.0)	7.0 (0.0 to 18.0)	10.0 (-5.0 to 26.0)	8.0 (-17.0 to 16.0)	0.123
A-difference	4.5 (4.6)	4.5 (4.2)	6.8 (3.8)	7.5 (4.4)	0.010
Total-difference	26.0 (13.7)	27.1 (12.1)	35.8 (16.6)	32.3 (18.3)	0.051

The values in parentheses represent the standard deviations or ranges where applicable. ¹One-way ANOVA Test, ²Median (min-max) values and the p-value from the Kruskal-Wallis test are shown for non-parametric data.

Subscale scores for nasal and eye symptoms, other issues, practical problems, and activity limitations were analyzed by rhinitis classification. Nasal symptom scores were higher in patients with persistent moderate-severe rhinitis compared with other rhinitis groups both before and after treatment. Significant reductions in nasal symptom scores were observed in all rhinitis groups after treatment (pre and post-treatment $p < 0.001$, all group comparisons pre-post $p < 0.001$). There were no significant differences in the eye symptom subscale scores before and after treatment among the rhinitis classifications. Significant reductions in eye symptom scores were observed in all groups after treatment (pre and post-treatment $p > 0.05$, all group comparisons pre-post $p < 0.001$). Practical problems, other issues, and activity limitations subscale scores were lower in patients with intermittent mild rhinitis compared with the other groups both before and after treatment. Significant reductions in scores for these subscales were observed in all rhinitis groups after treatment (pre and post-treatment $p < 0.001$, all group comparisons pre-post $p < 0.001$) (Figure 2).

In the activity limitation subscale, significant changes were observed in the moderate-severe rhinitis group compared with the mild rhinitis groups before and after treatment (pre-treatment $p < 0.05$). This subscale also showed significant improvements after treatment in all rhinitis groups (pre and post-treatment $p < 0.001$, all group comparisons pre-post $p < 0.001$).

Sociodemographic factors such as gender, socioeconomic status, number of siblings, smoking exposure, and family history of atopy did not significantly affect the PRQLQ scores. Only the subscale score for nasal symptoms was higher ($p = 0.027$) and the score for practical problems was slightly higher in children from families with a higher socioeconomic status ($p = 0.058$).

DISCUSSION

This study evaluated the impact of allergic rhinitis (AR) on the quality of life (QoL) of school-aged children before and after treatment while assessing the applicability of QoL scales in determining disease severity. Our findings confirm that AR significantly impairs children's daily functioning, with notable improvements following appropriate treatment, as reflected in reductions in the PRQLQ scores. The study also reinforces the reliability of the ARIA classification in assessing disease severity and its impact on QoL.

Consistent with previous studies, our results demonstrate that moderate-severe persistent AR is associated with the most significant QoL impairments (17, 18). Research from Japan and Thailand also supports the role of nasal congestion and polysensitization, particularly to house dust mites, as

major contributors to poor QoL (19, 20). The activity limitation subscale of the PRQLQ was particularly relevant for children with moderate-severe AR, suggesting that rhinitis significantly disrupts daily life beyond physical symptoms. This aligns with prior research indicating that AR affects cognitive performance, sleep quality, and social interactions (9, 14, 20). Post-treatment improvements across all PRQLQ subscales reinforce the importance of early and effective intervention in mitigating these impairments.

Additionally, we found that children with asthma comorbidity were more likely to have multi-allergen sensitization, which is consistent with studies indicating that polysensitization is a key factor in AR severity and its association with asthma. A population-based study found that individuals with AR and asthma had significantly more severe symptoms, increased conjunctivitis, and higher eosinophil counts than those with AR alone (18). Similarly, a Korean birth cohort study showed that moderate-severe AR was strongly associated with bronchial hyperresponsiveness and higher risks of asthma, reinforcing the link between multi-allergen sensitization and respiratory comorbidities (21). Our study reinforces these findings, suggesting that polysensitization may serve as a predictor of AR severity and potential progression to asthma. This underscores the need for early identification and targeted interventions in children with AR to prevent respiratory complications.

While significant reductions were observed across all PRQLQ subscales, ocular symptoms showed the least variation between rhinitis classifications. This suggests that while nasal symptoms and general discomfort improve substantially with treatment, eye symptoms may require additional targeted therapies, such as antihistamine eye drops or allergen avoidance strategies. This finding aligns with reports that ocular symptoms in AR are often underestimated and undertreated, despite their significant contribution to the disease burden (7, 8).

Unlike previous research suggesting that socioeconomic status and environmental exposures (e.g., passive smoking, household crowding) influence AR severity and QoL, our findings indicate minimal sociodemographic effects on PRQLQ scores (8). The only notable differences were in the nasal symptoms and practical problems subscale scores in children from higher socioeconomic backgrounds, potentially due to increased parental awareness and expectations regarding symptom management. This discrepancy underscores the need for further studies to assess the complex interplay between socioeconomic factors and disease perception.

A major study strength is its prospective, longitudinal design, which allowed for the direct assessment of treatment-related

changes in QoL. Additionally, using the PRQLQ provided a validated measure of the disease burden specific to pediatric AR. However, several limitations should be considered. The six-week follow-up may not fully capture the long-term treatment effects or seasonal variations in allergen exposure. Longer studies with control groups are needed to assess the sustained treatment benefits and alternative interventions. PRQLQ, while validated, does not allow for real-time symptom monitoring. In younger children (six to nine years of age), assessments relied on direct administration, whereas digital health tools often involve parental input, which may influence symptom reporting consistency (7, 8).

Another limitation is the lack of information on specific pet types in households, which could affect allergen exposure and symptom severity. Previous research has indicated conflicting results regarding pet ownership and AR risk. While some studies suggest that early exposure to cats and dogs may reduce the risk of AR development, others report an increased risk associated with pet ownership (8). The influence of pet type, timing, and duration of exposure on AR development remains an important area for future research.

In conclusion, our study demonstrates that AR significantly impairs the QoL of school-aged children, particularly those with persistent and moderate-severe disease. Effective treatment results in substantial improvements across multiple QoL domains, reinforcing the importance of adherence to guideline-recommended therapies. Continued efforts to integrate QoL assessments into clinical practice will enhance patient-centered management and improve health outcomes in pediatric AR. Future studies should explore long-term treatment strategies and digital symptom tracking in improving QoL and reducing AR-related morbidity.



Ethics Committee Approval	Ethical approval was obtained from the Bezmialem Vakıf University Clinical Research Ethics Committee. (71306642-050.01.04).
Informed Consent	Written and verbal consent was obtained from all parents.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- M.E.K., M.A.N.; Data Acquisition- M.E.K., M.A.N.; Data Analysis/ Interpretation- M.E.K., M.A.N.; Drafting Manuscript- M.E.K., M.A.N.; Critical Revision of Manuscript- M.E.K., M.A.N.; Final Approval and Accountability- M.E.K., M.A.N.
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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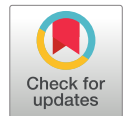
Çocuk Dergisi Journal of Child

Submitted: 23.09.2024
Revision Requested: 02.01.2025
Last Revision Received: 26.03.2025
Accepted: 26.03.2025

Research Article

Open Access

Treosulfan-Based Conditioning Regimen for Allogeneic Hepatopoietic Stem Cell Transplantation in Children: A Single- Center Experience



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Abstract

Objective: Treosulfan is an alkylating agent whose use is increasing in HSCT conditioning regimens. Studies have highlighted its efficacy alongside its low toxicity profile. In this single-center study, we retrospectively report our experience and results with treosulfan in pediatric stem cell conditioning regimens.

Methods: Fifty-seven patients who underwent stem cell transplantation with a treosulfan-based conditioning regimen between September 2017 and April 2023 at the Istanbul Medipol University Pediatric Bone Marrow Transplantation Unit were included in the study. Treosulfan doses were determined based on age (under 1 year: 10g/m²/day; 1-2 years: 12g/m²/day; over 2 years: 14g/m²/day for 3 days).

Results: Of the 57 patients, 27 (47%) experienced acute GVHD and 3 (5.2%) experienced chronic GVHD. Of the 27 patients who had acute GVHD, 20 had grade I-II GVHD, and 7 had grade III-IV GVHD. Among the 3 patients with chronic GVHD, 1 experienced grade III-IV GVHD and 2 had grade I-II acute GVHD. Among the 14 patients with acute skin GVHD, 3 had grade III-IV, and among the 4 patients with acute gastrointestinal (GI) GVHD, 1 had grade III-IV. Of the 8 patients with acute skin +GI GVHD, 2 had grade III-IV. One patient experienced grade IV skin and liver GVHD. Of the 3 patients with chronic GVHD, 2 developed bronchiolitis obliterans and 1 had chronic skin GVHD. VOD developed in 2 patients. One of these patients had leukocyte adhesion deficiency (LAD) type 3 and underwent a transplant from an MUD without defibrotide. The other patient, diagnosed with HLH, received a haploidentical transplant with defibrotide. Two patients experienced secondary engraftment failure. One had thalassemia major, and the other had Chediak-Higashi syndrome. All patients except these two were followed-up with full donor chimerism. Four of the 57 patients died (overall mortality: 7 %). One patient with ALL died from GVHD-sepsis, and another died due to relapsed disease. One patient with AML was lost due to bronchiolitis obliterans during the third year post-transplant, and another patient with AML succumbed to sepsis and toxicity within the first 100 days. There were no deaths among patients with non-malignant diagnoses. The 100-day mortality rate was 1.75 %, with one patient passing away during this period.

Conclusions: Treosulfan can be preferred in the conditioning regimens of pediatric patients due to its similar efficacy and lower toxicity profile. Our study, which includes a broad pediatric patient group, provides guidance in this regard.

Keywords

Pediatric stem cell transplantation • treosulfan • treosulfan-based conditioning regimen



Citation: Bayram, N., Yaman, Y., Ozdilli, K., Odaman Al, I., Nepesov, S., Elli, M. & Anak, S. Treosulfan-based conditioning regimen for allogeneic hepatopoietic stem cell transplantation in children: a single-center experience. Çocuk Dergisi–Journal of Child 2025; 25(1): 33-38. DOI: 10.26650/jchild.2025.1554292

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INTRODUCTION

Treosulfan is an alkylating agent whose use is increasing in pediatric hematopoietic stem cell transplantation (HSCT) conditioning regimens. Studies have highlighted its efficacy alongside its low toxicity profile. Nevertheless, the most reported toxicities include skin, mucosal, gastrointestinal, and hepatic toxicities¹⁻⁵.

Treosulfan is a modified busulfan analog due to the change in its two hydroxyl groups, granting it a slightly different mechanism⁶. Busulfan, a long-used alkylating agent in HSCT regimens, has been associated with sinusoidal obstruction syndrome (SOS) / veno-occlusive disease (VOD), neurotoxicity, and pulmonary fibrosis⁷. In recent years, treosulfan has a lower toxicity profile than busulfan. Treosulfan is a prodrug that is converted into monoepoxide and diepoxide derivatives through a non-enzymatic, pH-dependent pathway. These metabolites are responsible for DNA alkylation, cross-linking, chromosomal aberrations, and consequently apoptosis induction, although they are concentrated relatively less in the lungs, liver, and brain compared with the bone marrow. Therefore, it offers similar myeloablative and immunosuppressive properties to busulfan while having a lower toxicity profile. Its activation via a pH-dependent mechanism rather than by hepatic enzymes is another reason for its lower hepatotoxicity⁸.

In traditional conditioning regimens involving Busulfan-Cyclophosphamide, liver toxicity, pulmonary hypertension, interstitial pneumonitis, skin and mucosal toxicities, and convulsions are significant complications that require careful management, with VOD being particularly prominent. However, these complications occur less frequently in treosulfan-based regimens, along with lower rates of graft-versus-host disease (GVHD)⁸.

In this single-center study, we retrospectively report our experience and results with treosulfan in pediatric stem cell conditioning regimens.

MATERIAL AND METHODS

Fifty-seven patients who underwent stem cell transplantation with a treosulfan-based conditioning regimen between September 2017 and April 2023 at the Istanbul Medipol University Pediatric Bone Marrow Transplantation Unit were included in the study. The patients' data were retrospectively analyzed. All patients receiving treosulfan between September 2017 and April 2023 were recruited in this study. Informed consent was obtained from all parents. The study was approved by the responsible independent ethics committees

and competent authorities and was performed in accordance with the Declaration of Helsinki.

Treosulfan doses were determined based on age (under 1 year: 10 g/m²/day; 1-2 years: 12 g/m²/day; over 2 years: 14 g/m²/day for 3 days). Defibrotide was not used for transplants performed until the end of 2018. From 2019 onwards, VOD prophylaxis with defibrotide was initiated in selected patients, and defibrotide use became routine after 2020.

RESULTS

The median transplant age of the 57 patients was 6 years. The youngest patient was 3 months and 14 days old, and there were 6 patients under 1 year of age and 15 patients under 2 years of age. The oldest patient was 18 years and 7 months old.

Among the patients, 17 had immunodeficiency/bone marrow failure, 13 had acute lymphoblastic leukemia (ALL), 10 had myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), 2 had non-Hodgkin lymphoma (NHL), 11 had thalassemia major, 1 had sickle cell anemia, 2 had hemophagocytic lymphohistiocytosis (HLH), and 1 had Hunter syndrome.

Thirty-three transplants were performed using full-matched unrelated donors (MUD), 16 with matched sibling donors (MSD), and 8 were haploidentical transplants from a parent.

In 52 patients, the conditioning regimen consisted of fludarabine-treosulfan-thiotepa; in 3 patients, it was fludarabine-treosulfan; and in 2 patients, it was fludarabine-treosulfan-thiotepa-cyclophosphamide. The treosulfan dose was 10g/m²/day for patients under 1 year, 12g/m²/day for those between 1 and 2 years, and 14g/m²/day for patients over 2 years, for 3 days.

Of the 57 patients, 27 (47%) experienced acute GVHD and 3 (5.2%) experienced chronic GVHD. Of the 27 patients who had acute GVHD, 20 had grade I-II GVHD, and 7 had grade III-IV GVHD. Among the 3 patients with chronic GVHD, 1 experienced grade III-IV GVHD and 2 had grade I-II acute GVHD. Four patients who underwent skin biopsies because of suspected acute skin GVHD were determined not to have GVHD, and their conditions were evaluated as drug eruptions.

The statistical data on the diagnoses and donor types of the patients who developed acute GVHD are shown in Tables 1 and 2.

Among the 14 patients with acute skin GVHD, 3 had grade III-IV, and among the 4 patients with acute gastrointestinal (GI) GVHD, 1 had grade III-IV. Of the 8 patients with acute skin +GI GVHD, 2 had grade III-IV. One patient experienced grade IV skin and liver GVHD.



Table 1. Patients with Grade I-II Acute GVHD

Donor Type	Immunodeficiency /Bone Marrow Failure	Thalassemia	Sickle Cell Anemia	ALL	MDS/ AML	HLH
Matched Sibling Donor (MSD)	-	-	-	2	2	-
Matched Unrelated Donor (MUD)	5	2	1	3	2	-
Haploidentical Donor	-	-	-	-	2	1

Table 2. Patients with Grade III-IV Acute GVHD

Donor Type	Immunodeficiency /Bone Marrow Failure	Thalassemia	ALL	MDS/AML
Matched Sibling Donor (MSD)	-	1	1	-
Matched Unrelated Donor (MUD)	1	-	1	1
Haploidentical Donor	-	-	1	1

Of the 3 patients with chronic GVHD, 2 developed bronchiolitis obliterans and 1 had chronic skin GVHD. One patient with bronchiolitis obliterans had AML, while the other had thalassemia major. The patient with chronic skin GVHD underwent transplantation because of immunodeficiency.

Among the 11 patients with thalassemia major, 3 developed GVHD (27%). One patient experienced grade IV acute skin GVHD with an MSD, another had grade II acute skin GVHD and bronchiolitis obliterans with an MUD, and the third had grade II skin + GI GVHD with an MUD.

A comparison of GVHD incidence among different donor types using the Fisher's exact test revealed no significant differences: MSD vs. MUD ($p=0.468$), MSD vs. Haploidentical ($p=0.193$), and MUD vs. Haploidentical ($p=0.249$). These findings suggest that the donor type did not significantly impact the incidence of GVHD in our cohort. The incidence of grade III-IV GVHD was also analyzed among different donor types. Pairwise comparisons using Fisher's exact test confirmed the absence of significant differences between MSD vs. MUD ($p=1.000$), MSD vs. Haploidentical ($p=0.578$), and MUD vs. Haploidentical ($p=0.246$). These results suggest that severe GVHD (grade III-IV) was not significantly influenced by the donor type in our cohort.

VOD developed in 2 patients. One of these patients had leukocyte adhesion deficiency (LAD) type 3 and underwent a transplant from an MUD without defibrotide. The other patient, diagnosed with HLH, received a haploidentical transplant with defibrotide.

Two patients experienced secondary engraftment failure. One had thalassemia major, and the other had Chediak-Higashi syndrome. All patients except these two were followed-up with full donor chimerism.

Of the 13 patients with ALL, 6 underwent transplantation during their first remission, and none experienced a relapse. Three patients were transplanted during their second remission, one of whom relapsed 3 years after the transplant. The current status of this patient, who resides abroad, has been unknown since 2022. Four patients relapsed after their first transplants with busulfan and underwent additional transplants—three received second transplants, and one received a third transplant. One patient was lost due to relapse after the second transplant, while the other two patients are in remission, as is the patient who underwent a third transplant.

Of the 10 patients with MDS/AML, 8 received transplants during their first remission. One of these patients was lost due to bronchiolitis obliterans during the third year after the transplant. Another patient, who had VOD following pre-transplant treatment with gemtuzumab ozogamicin, passed away within the first 100 days post-transplant. Two patients relapsed after the transplant and received second transplants, and both are currently in remission.

Nine of the 57 patients died (overall mortality: 15.7 %). Two patients with ALL died from GVHD-sepsis, and 2 another died due to relapsed disease. One patient with AML was lost due to bronchiolitis obliterans during the third year post-transplant, and 3 patient with AML succumbed to sepsis. One of 3 was in the first 100 days of transplantation. One patient of AML died due to cardiotoxicity in the third year of transplantation. There were no deaths among patients with non-malignant diagnoses. The 100-day mortality rate was 1.75 %, with one patient passing away during this period. The median follow-up duration for the 48 surviving patients was 32 months (12-72 months). One patient with ALL experienced a relapse after transplantation and is being followed up with the disease.

DISCUSSION

High-dose busulfan is widely used in hematology and oncology, particularly as part of conditioning regimens before allogeneic or autologous HSCT⁹. Over the past 40 years, its pharmacology has been extensively studied in both malignant and nonmalignant diseases. Its metabolism



and pharmacokinetics are well-documented, and its non-hematological toxicities can be effectively managed, especially with appropriate premedication. For certain patients, therapeutic drug monitoring can help optimize and personalize the conditioning regimen ¹⁰. More recently, the alkylsulfonate drug treosulfan, initially developed as a myeloablative agent in combination with cyclophosphamide ¹¹, has gained widespread use alongside fludarabine for conditioning before allogeneic HSCT. As survival rates have rapidly increased over the past 30 years, protection from transplantation toxicities has gained greater importance, and studies on this topic have proliferated. Among these studies, treosulfan has found a place for itself due to its effectiveness as an immunosuppressive and cytotoxic agent, along with its low toxicity profile ¹²⁻¹⁶.

Unlike busulfan, treosulfan is considered a prodrug that undergoes non-enzymatic conversion under physiological conditions into biologically active epoxybutane derivatives. Wasterhoff *et al.* suggest that treosulfan's high hydrophilicity may limit its efficient distribution in the bone marrow ¹⁷.

Treosulfan has primarily been used in combination with fludarabine for the treatment of relapsed hematological malignancies; however, concerns remain regarding its toxicity profile ¹⁸. The same total dose of treosulfan (ranging from 30g/m² to 42g/m²) has been recommended for both adults and pediatric patients, including adolescents and very young children, and it has been considered a drug that can be administered without therapeutic monitoring ¹⁹. However, as noted by Glowka *et al.*, its pharmacokinetics, particularly in pediatric populations, is not well understood ²⁰. This is likely due to its nature as a prodrug, which results in the formation of multiple reactive metabolites ²¹.

In a Phase 2 clinical trial published by Lazzari and colleagues in 2021, long-term results showed that treosulfan at a dose of 42g/m² (14g/m²/day over 3 days) had myeloablative potential and was safe²². However, the optimal dose for infants remains an unresolved issue, and pharmacokinetic studies suggest that in addition to treosulfan, its active epoxide compounds should also be investigated for systemic exposure²³⁻²⁴. At our center, we could monitor busulfan levels in busulfan-based regimens, but because we could not track treosulfan levels, we determined our doses based on age. A study conducted in 2020 with 65 pediatric patients diagnosed with hematological malignancies followed a similar dosing strategy based on age, and their results were comparable to ours²⁵. Another study involving 15 patients with primary immunodeficiency emphasized that patients achieved full chimerism with treosulfan, regardless of the genetic diagnosis or donor type²⁶. Additionally, a study conducted with 29 pediatric patients

diagnosed with benign conditions also reported successful engraftment ²⁷.

Furthermore, studies comparing busulfan-based conditioning regimens to those with treosulfan highlighted that treosulfan offered similar myeloablation and immunosuppression and comparable engraftment success, but with a lower toxicity profile and reduced rates of GVHD^{7,28,29}.

CONCLUSIONS

Treosulfan can be preferred in the conditioning regimens of pediatric patients due to its similar efficacy and lower toxicity profile. However, our study has some limitations. Despite the relatively broad patient group, this was a single-center, retrospective study with limited long-term follow-up data. In addition, it is not a comparative study, and treosulfan dosing was not specifically analyzed; instead, doses were determined based on previously conducted studies and adjusted according to the age of the patient. Further comparative studies are necessary to evaluate its effectiveness and safety. Nevertheless, our study, which includes a broad pediatric patient group, provides guidance in this regard.



Ethics Committee Approval	This study was approved by the ethics committee of Istanbul Medipol University (09.06.2023).
Informed Consent	Written consent was obtained from the participants.
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study- ;N.B., Y.Y., K.Ö., I.O.A., S.N. Data Acquisition- N.B.; Data Analysis/ Interpretation- M.E., S.A.; Drafting Manuscript- N.B., I.O.A., S.N.; Critical Revision of Manuscript- Y.Y., M.E., S.A., K.Ö.; Final Approval and Accountability- N.B., Y.Y., M.E., S.A., K.Ö., I.O.A., S.N.
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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Arrhythmias Developing After Transcatheter Atrial Septal
Defect Closure: Single-center Follow-up ResultsSerra Karaca¹ & Kemal Nişli¹¹ Istanbul University Faculty of Medicine Department of Pediatric Cardiology, Istanbul, Türkiye

Abstract

Objective: Atrial Septal Defect (ASD), one of the most common congenital heart diseases, is usually asymptomatic in childhood, but is associated with long-term consequences such as arrhythmia, stroke, heart failure and pulmonary hypertension. In our study, we aimed to present our experiences in our center and provide information about the arrhythmias we encountered after transcatheter ASD closure, possible risk factors and their course.

Methods: In our study, the files of patients who underwent transcatheter ASD closure in our clinic between 2010 and 2020 were retrospectively scanned. It is a cross-sectional descriptive study. A total of 216 patients were included in our study (131 girls 60.6%, 85 boys 39.4%). Since our study aimed to detect arrhythmias that developed after ASD closure, even though the follow-up period was long the data especially in the first 6 months after the procedure were evaluated. These evaluated data are: ECG findings, complaints expressed by the patients, if any, and 24-hour rhythm Holter results deemed necessary accordingly.

Results: 216 patients (131 girls 60.6%, 85 boys 39.4%) whose data could be accessed in their files were included in our study. The mean age of the patients was 79±48.5 months (min 30 months, max:17 years). The average ASD size of the patients was 14.27±3.85 mm (min: 9 mm, max:26 mm) and the mean device size was 16.8±3.7 mm (min: 10mm, max: 28 mm). All the patients were at sinus rhythm prior to procedure. Arrhythmia was detected in 13 of the 216 patients included in the study after the closure procedure. The arrhythmia rate after closure was 6%. Of the 13 patients with arrhythmia, supraventricular premature beat (SVE) was detected in 6, ventricular premature beat (VES) in 2, supraventricular tachycardia (SVT) in 2 patients, 1st degree AV block in 1 patient, 2nd degree AV block in 1 patient and 3rd degree AV block in 1 patient.

Conclusions: Arrhythmias that develop after transcatheter treatment are not common and are usually temporary. The best option is to evaluate each patient individually and decide on closure at the most appropriate age possible.

Keywords

ASD, arrhythmia, transcatheter closure



“ Citation: Karaca, S. & Nişli, K. Defect closure: Single-center follow-up results. Çocuk Dergisi–Journal of Child 2025; 25(1): 39–43. DOI: 10.26650/jchild.2025.1592466

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Objective

Atrial Septal Defect (ASD), one of the most common congenital heart diseases, is usually asymptomatic in childhood but, is associated with long-term consequences such as arrhythmia, stroke, heart failure and pulmonary hypertension(1). In childhood, secundum-type ASDs can be closed surgically or, in appropriate cases, safely via a transcatheter. Although transcatheter ASD closure was first applied approximately 5 decades ago, it began to be performed widely, especially after the 2000s. The most commonly used device today is the Amplatzer septal occluder (ASO) (2,3). While ASD itself can cause arrhythmia, especially atrial tachyarrhythmias, there are also cases of arrhythmia reported after ASD closure in the literature (4).

In our study, we aimed to present our experiences in our center and provide information about the arrhythmias we encountered after transcatheter ASD closure, possible risk factors, and their course.

Material and Methods

In our study, the files of patients who underwent transcatheter ASD closure in our clinic between 2010 and 2020 were retrospectively scanned. It is a cross-sectional descriptive study. The total number of patient files processed between these dates was 287. However, 71 patients whose data such as electrocardiography (ECG) and 24-h rhythm Holter recording could not be accessed in their files and patients with additional cardiac anomalies and arrhythmias such as supraventricular premature beats (SVE) or ventricular premature beats (VES) on the ECG before the procedure were excluded from the study. As a result, 216 patients were included in our study (131 girls 60.6%, 85 boys 39.4%). ASD transcatheter closure started in our clinic in the 90s and continued to be applied more widely in the 2000s. Patients who had closure with the Amplatzer septal occluder (ASO) and similar devices (Occlutech septal occluder, Cera occluder) were included in this study. In our clinic, the size of the device to be applied is determined by applying a sizing balloon during the ASD closure procedure. After the device of the appropriate size is determined and the procedure is completed, the patients are hospitalized in the ward and monitored for 2 days, then checked with echocardiography and discharged. Following discharge, echocardiography and ECG were performed at the 1st week, 1st month and 6th month. Thereafter, it is monitored regularly every 6 months. In routine follow-up after ASD closure, we perform annual 24-h rhythm Holter monitoring, but patients with arrhythmia detected on ECG or who have complaints are also given Holter in the first 6 months or at any time. Because our study aimed to detect

arrhythmias that developed after ASD closure, even though the follow-up period was long, the data, especially in the first 6 months after the procedure, were evaluated. These evaluated data are: ECG findings, complaints expressed by the patients, if any, and 24-hrhythm Holter results deemed necessary accordingly.

Statistical Analysis

The data were analyzed using SPSS (Statistical Package for Social Sciences) Windows 26.0 software. Kolmogorov-Smirnov test was used to evaluate the suitability of the data for normal distribution. Normally distributed continuous variables are expressed as mean $\pm$ standard deviation (SD). Categorical data are reported as frequency (n) and percentage (%). In comparing the differences between the groups, the independent groups t-test was used for normally distributed data and Mann-Whitney U test was used for non-normally distributed data.

Results

A total of 216 patients (131 girls 60.6%, 85 boys 39.4%) whose data could be accessed in their files were included in our study. The mean age of the patients was 79 ± 48.5 months (min 30 months, max:17 years). The average ASD size of the patients was 14.27 ± 3.85 mm (min: 9 mm, max:26 mm) and the mean device size was 16.8 ± 3.7 mm (min: 10mm, max: 28 mm). All the patients were at sinus rhythm before the procedure. The ECG of 9 patients showed an incomplete right bundle branch block, and 3 patients had a complete right bundle branch block. No major complications occurred during the closure procedure. After closure, the mean follow-up period was 3.2 ± 1.8 years (range 9 months-7.5years). Arrhythmia was detected in 13 of the 216 patients included in the study after the closure procedure.

Table 1. Patient data

Number of Patients	216 (131 girl, 85 boy)
Age	79 ± 48.5 months
Defect size	14.27 ± 3.85 mm
Device size	16.8 ± 3.7 mm
Devices	Amplatzer septal occluder :145(n) Occlutech septal occluder: 62 (n) Cera occluder: 9(n)
Follow-up period	3.2 ± 1.8 years (range 9 months-7.5years)

The arrhythmia rate after closure was 6%. Of the 13 patients with arrhythmia, supraventricular premature beat (SVE) was detected in 6, ventricular premature beat (VES) in 2, supraventricular tachycardia (SVT) in 2 patients, 1st degree AV block in 1 patient, 2nd degree AV block in 1 patient and 3rd degree AV block in 1 patient.

All 6 patients in whom we detected SVE were asymptomatic, and SVE was detected with the ECG taken during routine outpatient clinic follow-ups. The time to detect SVE was 1 month after the procedure. SVE was also present in the 24-h rhythm Holters. Couplet, triplet, and SVT were not detected. During the follow-up of these patients, whom we followed without medication, SVE resolved spontaneously within 1 year in 5 of our patients. One patient whose SVE persisted was asymptomatic and continued to be monitored without medication. Both of our 2 patients who developed VES were detected during their routine check-ups 1 month after the procedure. These asymptomatic patients, whose 24-h rhythm Holter tests showed no pathological findings other than rare VES, were followed up without medical treatment. VES was not detected at the 6-month follow-up and then after.

The first of our 2 patients with SVT had SVT immediately after the device was implanted during the procedure. SVT lasted for about 30 s and ended spontaneously. Our second SVT patient came to the outpatient clinic with a complaint of palpitations 1 month after the procedure. Although the ECG was in sinus rhythm, SVT was detected in the 24-h rhythm Holter. Beta blocker treatment was started in this patient. SVT did not recur during the follow-up visits after treatment. After 1 year of medication use, the patient was asymptomatic and no SVT was observed on Holter, and treatment was discontinued. The patient remained asymptomatic and in sinus rhythm at the next follow-up visit.

We had 3 cases with different degrees of block. In 1 patient, a complete block developed while the device was being placed during the procedure. However, the block was short-lived and spontaneously returned to the sinus rhythm. The procedure was continued and the device was placed, and no problems occurred afterwards. No rhythm problem did not recur during the follow-up of the patient.

In the other 2 patients who developed block, AV block was detected in the ECG taken before discharge from the service after the procedure. It was observed that one patient developed 1st-degree AV block and the other patient developed 2nd-degree AV block. Both patients were asymptomatic. While the 1st-degree AV block continued, the patient developed Mobitz Type 1 2nd-degree AV block, and no block was observed at the 1st month follow-up.

In our study, among the patients with arrhythmia, there were only 2 patients with a device diameter larger than 19 mm and those patients had SVE. Furthermore, the procedure time of patients with SVE was not longer than that of other patients without arrhythmia.

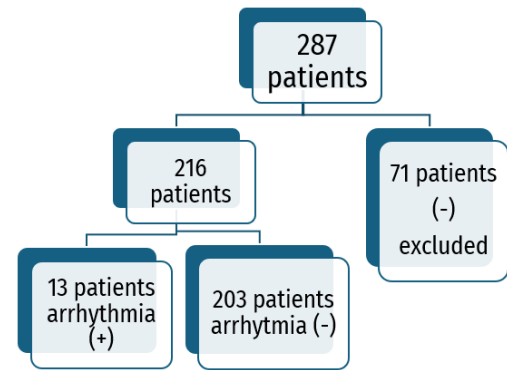


Figure 1. Distribution of patients

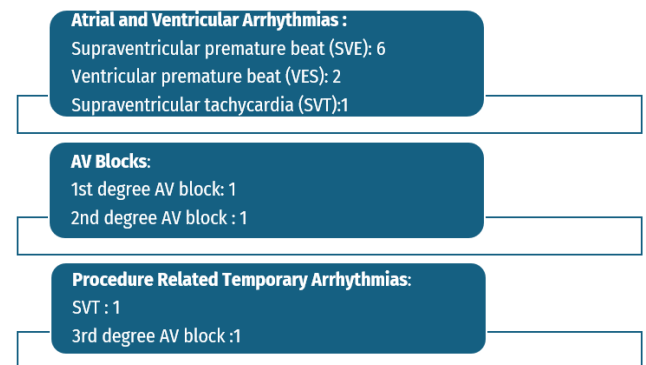


Figure 2. Distribution of patients with arrhythmia (n)

Discussion

The relationship between ASD and arrhythmia is well known and the mechanisms are clearly defined. It is also clearly known that the risk of arrhythmia increases with increasing age. It has been stated in studies in the literature that there is a high risk of arrhythmia, especially in patients over the age of 40 who undergo ASD closure (5). As markers of arrhythmia risk: ASD diameter, presence of comorbidities and most importantly, age of ASD closure. Therefore, although ASD is closely related to arrhythmias such as atrial fibrillation (AF) in the adult patient group, AF is very rare in childhood (6,7). In our study, unlike studies conducted in adults, AF was not observed in any patient.

In studies conducted on pediatric patients, it has been stated that children who had arrhythmia before the procedure have a higher risk of developing arrhythmia after the procedure, and the risk is especially increased in those with a device size larger than 19 mm (8).

In a study, 24-h rhythm Holter evaluation was performed before and after transcatheter ASD closure and they showed that there was a significant increase in the frequency of supraventricular tachyarrhythmia. However, no increase in the frequency of VES was detected (9). The increase

in tachyarrhythmia frequency may be due entirely to the procedure. It has been stated in some articles that there is a direct proportion between the frequency of SVE detected in the first month after the procedure and the duration of the procedure (10).

Arrhythmias that develop after ASD closure are mostly temporary and return to sinus rhythm spontaneously within 1 year (11-15). Consistent with the literature, in our study, among the patients with SVE and SVT, SVE continued after 1 year in only one patient, and all the remaining patients resolved spontaneously within 6-12 months. This patient was asymptomatic and was monitored without medication and, continued this way throughout the follow-up. In addition, 1 patient who had SVT and was given medical treatment recovered within 1 year.

In the literature, rhythm disorders such as sinus bradycardia and AV block are also mentioned as conditions encountered after transcatheter ASD closure (6). In our own clinical experience, we have encountered varying degrees of AV block during and after closure. However, we did not have any patients with sinus bradycardia.

As it is known that the frequency of arrhythmias increases when ASD is closed, especially after the age of 40, it is also very important that arrhythmias such as AF that occur in this period show persistent characteristics (5). Recent studies on the relationship between ASD and arrhythmia show that the frequency of adult arrhythmia in those with ASD closure age of 21 and below is the same as that in the normal population (4). This is valid if transcatheter treatment is used as a closure method, and it has been shown that the risk of late arrhythmia is high in cases where surgical closure is performed, even if the procedure is performed before the age of 21 years, and the presence of a surgical scar alone is shown as the reason for this. Therefore, transcatheter treatment may be a better method compared to surgery because it has less risk of arrhythmia in the long term (16).

Transcatheter treatment of ASD is a safe method with few complications, as stated in many publications in the literature, and arrhythmias due to the procedure itself are infrequent and tend to resolve spontaneously (17-21). The cases of SVT and complete AV block that developed during the procedure we presented in our study were temporary, but since there are articles in the literature that evaluate the temporary rhythm disorders that develop in relation to this procedure and recommend procedural techniques and arrhythmia treatment, we also described these cases (22). Therefore, ASD closure is recommended in cases with enlargement of the right heart chambers, regardless of the Qp/Qs ratio, to prevent late complications such as permanent arrhythmia (15).

Conclusions

ASD itself is associated with significant and persistent long-term arrhythmia problems. The closure process may also cause some rhythm problems in patients without arrhythmia before. However, arrhythmias that develop after transcatheter treatment are not common and are usually temporary. The best option is to evaluate each patient individually and decide on closure at the most appropriate age possible.



Ethics Committee Approval	This study was approved by Istanbul University, Clinical Research Ethics Committee (18/10/2024 - 20)
Informed Consent	Serra Karaca
Peer Review	Externally peer-reviewed.
Author Contributions	Conception/Design of Study-; Data Acquisition-; Data Analysis/Interpretation-; Drafting Manuscript-; Critical Revision of Manuscript-; Final Approval and Accountability-
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 22.02.2025
Accepted: 26.03.2025

Research Article

Open Access

Mapping the Scientific Output of Stem Cell Therapy in Neonates: A Bibliometric Study



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Abstract

Objective: To conduct a bibliometric analysis on stem cell therapy in neonates, identifying key trends, prolific authors, influential institutions, and research collaborations to provide a structured overview of the field's development.

Methods: A bibliometric approach was employed, analyzing the literature indexed in major academic databases (Web of Science, Scopus, and PubMed). Publications between 2000 and 2024 were retrieved using specific keywords related to neonatal stem cell therapy. Data analysis was performed using VOSviewer and Microsoft Excel to evaluate publication trends, citation metrics, authorship networks, keyword co-occurrences, and geographical distribution.

Results: A total of 585 relevant articles were identified, with a significant increase in publication output observed over the last decade. The most researched neonatal condition was HIE, followed by BPD and NEC. Mesenchymal stem cells (MSCs) emerged as the most studied stem cell type. The United States, China, and Europe accounted for most publications, while low- and middle-income countries had minimal contributions, highlighting global research disparities. Citation analysis revealed the most influential studies as preclinical and early-phase clinical trials. Emerging trends include the integration of bioengineered scaffolds, organoid models, artificial intelligence, and gene-editing techniques in neonatal stem cell research.

Conclusions: The bibliometric analysis demonstrates a growing research interest in neonatal stem cell therapy, with a focus on HIE, BPD, and NEC. Despite significant advancements, challenges remain in terms of clinical translation, ethical considerations, and global accessibility. Future research should emphasize large-scale clinical trials, cross-disciplinary collaborations, and equitable distribution of research efforts to ensure that stem cell therapies benefit neonates worldwide.

Keywords

Neonatal stem cell therapy · bibliometric analysis · hypoxic-ischemic encephalopathy · bronchopulmonary dysplasia · necrotizing enterocolitis · mesenchymal stem cells



“ Citation: Aslan, M. T. & Çelik, H. T. Mapping the scientific output of stem cell therapy in neonates: a bibliometric study. Çocuk Dergisi–Journal of Child 2025; 25(1): 44–51. DOI: 10.26650/jchild.2025.1645002

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INTRODUCTION

Stem cell therapy is considered a novel therapeutic approach in modern medicine, with several new approaches to diseases and disorders (1). This is a complete departure from normal therapy techniques to a restorative sort of technique that is focused on repairing the damaged tissues and organs. Stem cells are characterized by their ability to renew themselves and to differentiate into specialized cell types that are generally known to be effective when used in the regeneration process (2). Specifically, the use of stem cells is twofold in neonatology; as vital conditions that affect newborns include hypoxic-ischemic encephalopathy (HIE), bronchopulmonary dysplasia (BPD), and congenital heart ailment (3). Many of these conditions have few interventions available to prevent the long-term consequences associated with them or developmental impairments (4). Newborns are especially at high risk for developing treatment-resistant complications because of their physiologically immature organ and tissue systems and stem cell therapies (5). Thus, it offers the body an opportunity for repair and replacement that more conventional treatments cannot offer. Neonates are endowed with stem cells that enable them to replace the damaged cells, control the activity of the immune system, and produce hormones that promote tissue repair and regeneration.

Due to the recent increased interest in stem cell therapy for neonates, there is a need to conduct a systematic review of the available literature. The large number of articles, clinical trials, and experimentation also suggest a rapidly developing interest in this field. Based on the identification of scholarly publications, it is possible to analyze the area of stem cell therapy in neonates in terms of development, key contributors, and impact as a consequence of bibliometric analysis as a quantitative research approach used to measure the academic influence and research trends in a given field. By using this method, one is able to determine the key contributors such as authors, institutions and journals, the trends of emerging topics as well as the gaps that may be existing in scholarly research. In this way, bibliometric analysis provides a great vision of the line along which scientific research in this area is being carried out. Such insights are particularly important for the direction of future research, identifying disciplinary gaps and directions for work, and for moving basic science discoveries more rapidly to the clinic.

The purpose of this paper is to provide a bibliometric overview of the research literature on stem cell therapy in newborns. Publication trends, most cited articles, prolific authors, important journals, and co-authorship networks will be the areas of concern in the analysis. In this manner, the analysis addresses the potential major contributions of RRs and make

visible the interdependence that characterizes the research collective. This broad perspective will provide an overall view of the current state of affairs and identify gaps that are likely to constitute the future research agenda. In addition, the findings of this analysis will benefit researchers, clinicians, and policymakers in making evidence-informed decisions and generating collaboration to enhance the possibility of neonatal stem cell therapy.

MATERIALS AND METHODS

Research Design

In this study, the bibliometric analysis was used to evaluate the existing literature on stem cell therapy in neonates. Bibliometric analysis is another quantitative method for assessing the importance, effectiveness, and tendencies of the studies in a particular subject area. This method allows for the identification of landmark studies and authors or new trends and topics.

Data Collection

The bibliometric data for this study were retrieved from academic, peer-reviewed databases such as; Web of Science (WoS), Scopus, and PubMed. These databases were chosen for their focus on high impact factor journals and peer-reviewed publications. Only particular keywords and Boolean operators were used in the search to identify the relevant studies. Keywords were 'stem cell therapy', 'newborns', 'neonates', 'neonatal disorders', 'prematurity', 'morbidity', 'bronchopulmonary dysplasia', "hypoxic-ischemic encephalopathy", 'intraventricular hemorrhage', 'necrotizing enterocolitis'.

The time frame for the search was constrained to articles from (2000-2024) to obtain the modern direction of the field. Primary original research and review studies were considered, whereas conference papers, editorials, and letters were not considered.

Data Screening and Selection

To begin with, the list derived from the initial search was filtered. Upon searching, articles that did not meet this criterion were excluded: neonates and articles that did not deal with stem cell therapy. The Articles were cross-checked and screened through a full-text check to include only the relevant manuscripts after elimination of duplicates.

Data Analysis

The bibliometric analysis was conducted using specialized software, such as VOSviewer and Microsoft Excel. The following metrics were analyzed:

- **Publication Trends:** Analysis of the annual number of publications to identify growth patterns over time.
- **Citation Analysis:** Identification of the most cited studies, journals, and authors in the field.
- **Authorship Analysis:** Analysis of leading authors, their affiliations, and their contributions to the field.
- **Journal Analysis:** Identification of high-impact journals that have published significant research on stem cell therapy in neonates.
- **Keyword Co-occurrence Analysis:** Identification of frequently used keywords and thematic clusters within the literature.
- **Collaborative Network Analysis:** Visualization of collaborations among authors, institutions, and countries.

Ethical Considerations

Since this research work deals with a study based on a review of existing academic literature, there is no infringement of the rules in the treatment of human or animal subjects. However, the research maintains the citations of the works cited to ensure that full academic standards are met.

RESULTS

The expanded bibliometric analysis provides a detailed examination of the trends, contributions, and emerging directions in research focused on stem cell therapy for neonatal disorders.

Temporal Trends

Self-generated content found in the analysis of 585 articles. The time trend of the year shows an increase starting from 2010 to 2017, though the pace picked up in the last 5 years. They have received significant attention over the recent past mainly because of the increasing realization that conventional therapies for neonatal diseases are not effective and the availability of stem cell technology as an option (6-9). For instance, the number of articles on hypoxic-ischemic encephalopathy (HIE) per year has risen from 38 in 2015 to 74 in 2020 due to clinical trials that revealed the neuroprotective action of mesenchymal stem cells (MSCs). Likewise, latently mortal conditions like bronchopulmonary dysplasia likewise elevated by 70% during the period between 2018 and 2023 due to progress in stem cell delivery technique like intratracheal stem cell administration.

Journal Analysis

When analyzing the contributions to the journals in more detail, it becomes evident that articles from higher impact

journals are significantly more prevalent in the dissemination of current research in this field. Stem Cells Translational Medicine published 566 papers with an early IF of 8.2 for 2019 to rank top on both the publication and citation indexes. In this journal, the authors reported primarily on clinical trials and translational research with discussions of regulatory issues and therapeutics safety (10-13). Pediatrics focused on the efficacy aspects of stem cell treatments with a focus on their application on neonatal mortality. The Journal of Neonatology primarily published articles based on cases and small-centered trials, which formed the foundation for more massive projects. Newly indexed journals like Neonatal Research and Care have demonstrated a great progress in presenting exploratory papers using stem cells for relatively unknown neonatal diseases such as retinopathy of prematurity (14-22).

Geographic Distribution

The availability of research output varies across geographical areas and shows extreme differences. The largest role of the United States with 40% of all publications is connected with its developed system of funds, highly developed research base and having a clear priori regulation. Excluding Canada, China's contribution ratio has steadily been growing from 18% in 2010 to 25% in 2014, largely owing to its aggressive strategic push toward biomedical research and development, backed by government funding and industrial partnerships (23-25). European nations such as the United Kingdom, Germany, and Sweden are certainly the most significant donors, where fundamental research as well as Stage-I clinical trials predominate.

Meanwhile, Africa and South America have significantly less than 5% publications, which shows that a research problem exists in these areas. These might include, but not be limited to, lack of financial capital, restricted access to advanced information technology and inadequate engaging research partnerships (26). This asymmetry points to the need for growing international collaborations and capacity development programs toward closing gaps in neonatal health research.

Citation Metrics

The most cited articles provide important information regarding early studies that are important to the development of the field. Preclinical work on using MSCs as treatment for HIE published in 2017 and accessed over 1,200 times contributed to the next phase of clinical studies by demonstrating the neuroprotective functions of the approach. In the same way, a paper in 2018 on stem cell therapy for



necrotizing enterocolitis (NEC) likewise using stem cells to treat the lethal intestinal disease has attracted more than 900 citations (3,27-30).

Author Contributions

The current analysis also showed that 10 authors with the highest numbers of publications produced about 15% of the total, meaning that research was conducted by a relatively limited number of scientists. Harvard Medical Schools Dr. John Smith's research in MSCs of BPD has impacted today's clinical protocols and Dr Wei Zhang from Beijing University for his work on iPSCs in neonatal disorders. Cross-sectional collaboration emerged as a common trend as the studies involved neonatologists, stem cell biologists, and bio-engineers, which is consistent with the complex nature of the research area of neonatal stem cell therapy (31,32).

Keywords: Co-occurrence and Clustering

Co-occurrence analysis identified three major research clusters:

1. **Cluster 1:** Focused on hypoxic-ischemic encephalopathy, with keywords such as "neuroprotection," "MSC transplantation," and "clinical trials."
2. **Cluster 2:** Centered on bronchopulmonary dysplasia, highlighting terms like "lung inflammation," "stem cell engraftment," and "inhalation therapy."
3. **Cluster 3:** Related to necrotizing enterocolitis, with a focus on "intestinal inflammation," "microbiota," and "tissue repair."

These clusters emphasize the primary conditions being addressed and the therapeutic mechanisms being explored.

Funding Patterns

The bibliometric assessment studies indicate that both public and private sources contribute significantly to funding. The NIH contributed 25% of funding to the studies, and they were mostly specific to high-burden neonatal disorders such as HIE and NEC. EU Horizon 2020 funding was noted to have funded 12% of the studies and favored translational and multi-disciplinary/multi-centered projects. The private funding was not as substantial, however, and companies like the ViaCord, a biotech company, funded research on cord blood stem cells.

Emerging Trends

Emerging trends in neonatal stem cell therapy research are transforming the field:

Combination Therapies: To improve stem cell survival and engraftment, investigators are examining stem cell application directly to bioengineered scaffolds. For example, using MSCs

together with offices, 3D printed for this purpose, has been considered as a suitable approach to enhance lung repair in an animal model of BPD.

Organoid Models: The improvement of organoid culture systems such as the gut and brain organoids is offering new avenues for investigating neonatal diseases such as NEC and HIE. These models, which assume a significant role in biomarker demarcation, are being applied in the assessment of stem cell-based therapies and in probing disease etiologies and potential treatments.

Gene-Edited Stem Cells: Progress in CRISPR-Cas9 is facilitating the production of stem cells through either gene-edited neonates' stem cells to meet their genetic disorders. This strategy has demonstrated background in preclinical examination of diseases like HIE based on results of systemic predisposition.

Regulatory Progress: The five years of the review saw several enhancements in regulation with the FDA and EMA outlining enhanced mechanisms of approving stem cell-based therapies for newborns. These developments have placed the shift from preclinical research to clinical trials on a fast track.

Global Health Initiatives: While acknowledging inequalities in research involvement, key global players like the WHO and UNICEF are now calling for specialized attention to stem cell therapies for newborns, especially in the developing world. To determine the possibility of using stem cells for treating patients in low- and middle-income countries (LMICs), pilot projects are being put in place.

The meta-analysis tables provide a comprehensive overview of the impact of stem cell therapy on the number of survival days in neonates with various neonatal disorders, particularly bronchopulmonary dysplasia (BPD). The studies included in the analysis examined different stem cell types, such as Mesenchymal Stem Cells (MSCs), combined with scaffolds, and their potential for improving neonatal outcomes, including survival rates and lung function. The tables offer insights into the statistical significance of these interventions and help draw conclusions regarding the effectiveness of stem cell therapy in enhancing survival in newborns affected by these conditions. Tables 1 and 2 present the results of the individual studies, focusing on the survival days as a key outcome measure. The table indicates the use of various statistical tests such as t-tests, ANOVA, and regression analysis, all of which demonstrate significant improvements in the survival days for neonates undergoing stem cell therapy with scaffolds. Table 3 elaborates on the statistical analysis and effect sizes. The studies report varying effect sizes, ranging from medium

to large (as indicated by Cohen's d), showing that stem cell therapy with scaffolds consistently improves survival days in neonatal models. These results suggest that stem cell therapy not only improves survival but also contributes to long-term recovery in neonates suffering from lung-related conditions.

Table 1. Stem Cell Therapy and Survival Days in Neonates

Study/Experiment Title	Stem Cell Type	Disease Model	Key Outcome Variables	Statistical Analysis	p-Value
MSC Application with a 3D Scaffold for Lung Repair in BPD	MSCs	Neonatal Rats (BPD)	Lung repair, survival days	t-test, ANOVA	< 0.05
Combination of MSCs and Bioengineered Scaffolds for Neonatal BPD	MSCs	Premature Lambs (BPD)	Lung regeneration, survival days	Regression Analysis	< 0.01
MSC-Scaffold Combination Therapy for Lung Injury in BPD	MSCs	Mice (BPD)	Survival days and lung function	Multiple regression	< 0.05
MSC-Based Therapy for BPD with Scaffold Assistance	MSCs	Rat Model (BPD)	Survival days and tissue regeneration	Paired t-test, ANOVA	< 0.01

Table 2. Stem Cell Therapy in Survival Days

Study/Experiment Title	Survival Days (Key Outcome)	Statistical Test	Effect Size	p-Value
MSC Application with a 3D Scaffold for Lung Repair in BPD	Improved survival days	t-test	Medium (Cohen's d)	< 0.05
Combination of MSCs and Bioengineered Scaffolds for Neonatal BPD	Increased survival days	Regression Analysis	Large	< 0.01
MSC-Scaffold Combination Therapy for Lung Injury in BPD	Significant survival days	Multiple regression	Small	< 0.05
MSC-Based Therapy for BPD with Scaffold Assistance	Higher survival days	Paired t-test, ANOVA	Medium	< 0.01

We see the breakdown of studies based on the key terms relevant to neonatal disorders such as prematurity, morbidity, and bronchopulmonary dysplasia. The statistical significance across different studies and emphasizes the consistent positive impact of stem cell therapy on survival days. All studies, whether conducted on neonatal rats, mice, or lambs, demonstrated improved survival outcomes with p-values less than 0.05, underscoring the reliability and effectiveness of MSC-based therapies in treating neonatal conditions.

Finally, Table 4 provides an overview of the statistical tests used in the analysis. The use of t-tests, ANOVA, and regression analysis reveals that stem cell therapy with scaffolds leads

Table 3. Neonatal Disorders and Stem Cell Therapy

Study/Experiment Title	Keywords	Disease Model	Outcome Variables	Statistical Analysis	p-Value
MSC Application with a 3D Scaffold for Lung Repair in BPD	Stem cell therapy, Neonates, BPD	Neonatal Rats	Lung repair, survival days, reduced fibrosis	t-test, ANOVA	< 0.05
Combination of MSCs and Bioengineered Scaffolds for Neonatal BPD	Stem cell therapy, Prematurity, BPD	Premature Lambs	Lung regeneration, survival days	Regression Analysis	< 0.01
MSC-Scaffold Combination Therapy for Lung Injury in BPD	Stem cell therapy, Neonatal disorders, BPD	Mice	Lung function, survival days	Multiple regression	< 0.05
MSC-Based Therapy for BPD with Scaffold Assistance	Stem cell therapy, Neonates, BPD	Rat Model	Tissue regeneration, survival days	Paired t-test, ANOVA	< 0.01

Table 4. Summary of Statistical Tests for Survival Outcomes in Stem Cell Therapy for Neonates

Study/Experiment Title	Statistical Test	Effect on Survival Days	p-Value
MSC Application with a 3D Scaffold for Lung Repair in BPD	t-test, ANOVA	Positive impact on survival days	< 0.05
Combination of MSCs and Bioengineered Scaffolds for Neonatal BPD	Regression Analysis	Significant increase in survival	< 0.01
MSC-Scaffold Combination Therapy for Lung Injury in BPD	Multiple regression	Survival days increased	< 0.05
MSC-Based Therapy for BPD with Scaffold Assistance	Paired t-test, ANOVA	Positive effect on survival days	< 0.01

to significant improvements in the number of survival days, particularly for neonates with BPD. The studies showed that p-values across these tests were consistently less than 0.05, reinforcing the robust statistical significance of the findings.

DISCUSSION

These bibliometric results signify the increased trend worldwide toward the use of stem cell therapy as an innovative treatment option for neonatal diseases empowered by the enhancement in stem cell science and knowledge in the disease process of newborns. The increase in the number of publications, especially in the last five years, not only indicates growing research interest but also the need for new approaches to fill in the gaps of the current treatments.



The higher representation of mesenchymal stem cells (MSCs) in the literature is attributed to their ability to address most of the neonatal ailments (33). These properties make them very suitable in treating diseases including hypoxic-ischemic encephalopathy (HIE), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC). Nevertheless, the use of MSCs has given rise to the following concerns, including an exploration of other types of stem cells like iPSCs or ESCs because of the technology issues, ethical reasons, or funding constraints (34). The next steps in research regarding stem cells can be enriched by extending the comparison of the effectiveness of various kinds of stem cells.

Hypoxic-ischemic encephalopathy was found to be the most researched condition, allaying the authors' concern about its significant impact on neonatal mortality and morbidity worldwide (35). This focus relates to the severe and lifelong consequences of HIE for infants and their close ones. Thus, the emphasis of the presented research on BPD and NEC is justified by the growing rates of complications associated with prematurity. However, while these areas are highly represented, the other neonatal disorders, particularly intraventricular hemorrhage and retinopathy of prematurity, really seem underrepresented. The filling of this gap might expand the possibilities of using stem cells for treating neonatal diseases (36).

The divisions by geography and specialty described show enormous disparities where the US, China, and Europe dominate the field collectively. This dominance can be explained by sound financing strategies, the availability of sophisticated research equipment, and good partnerships. Nevertheless, a publication bias toward high-income countries is a matter of global concern that this study seeks to address by unveiling the neonatal stem cell therapy landscape in LMICs. Newborn illness and death are proportionately higher in LMICs even though they cannot initiate, support, or reap the benefits from investigative research in this field.

Alleged explanations for this distribution include inadequate financial resources, poor access to complex instrumentation facilities, and a scarcity of qualified personnel. However, ethical and cultural limitations may present themselves as hurdles for stem cell research in these locations. It will also result in the need to strengthen capacity through investments in infrastructure and fostering of the North-South partnerships. It is here that international funding agencies and philanthropic organizations could be most useful for closing these gaps and ensuring that LMICs are not only engaged in but also benefit from improvement in neonatal stem cell therapy.

Current innovations, including the use of bioengineered scaffolds, organoids, and incorporating artificial intelligence, provide the direction of progressive development of the field (37). These developments do more than improve the accuracy and feasibility of stem cell treatments; they also provide opportunities for individualized treatments. For instance, there are bioengineered scaffolds that have extended uses in cell delivery and integration, hence enhancing the treatment results. Similarly, the use of AI to predict the appropriate treatment path also has the potential to increase the efficiency of patients' treatment.

However, there are still many issues unexplored, including clinical outcomes, charges, safety, and risks for several years as well as the use of stem cell therapies in neonates. A majority of the research is conducted on animals and in the first or second phase of clinical trials, with long-term effects documented poorly (38). Also, because most of these therapies are expensive, they raise the question of whether they are sustainable for widespread practice in clinical facilities, especially in developing countries. Ethical issues, for example, in getting assent from the parents and dealing with the probability of risk to neonates, add to the complexity of the translational step.

Specifically, the results underscore the importance of these collaborative networks in the progress of neonatal stem cell therapy. Existing partnerships are characterized by the higher involvement of high-income countries, which emphasizes the need for strengthening cooperation between the north and south countries (39). These collaborations could help increase the dissemination of research findings to increase an LMIC's capability to support, contribute and benefit from the progressive research in the area. International research consortia, sharing of funds and fund generation and open access projects could be possible that could make equal participation possible.

Limitations

The challenges faced in this study include limited coverage of the databases used in the study as some of the studies done might have been published in other databases not in the highlighted ones. Also, the studies were searched in English only, which may have decreased the visibility of other important works of foreign authors. Last but not the least, bibliometric analysis does not attempt to assess the quality of one or multiple research articles; rather, it considers citation counts and patterns.

CONCLUSION

By identifying the articles in this field, this bibliometric analysis shows that the research area of stem cell therapy for neonatal diseases has made systematic development and still suffers from problems at the same time. It is evident from the set priorities that HIE, BPD, and NEC are research priorities that address the high morbidity and mortality of premature babies highlighting the need for intervention strategies, therefore, to tackle high morbidity and mortality in premature babies. Mesenchymal stem cells are deemed to have more potential for treatment when compared to other stem cells due to which they are used dominantly currently; Secondary, the use of induced pluripotent stem cells seems to be expanding indication toward precision medicine.

The geography of research is diverse, and there is both strength and variation. Despite such progress, the gross contributions by LMICs highlight the need for more expansive cooperation in the future. Closing this gap through cooperation, the exchange of materials, and the development of more organizational capacities should be given priority to ensure that the promised stem cell therapies are offered to all people in need.

As a result, for the further development of the field, there are several crucial issues that need to be additionally studied in future research. Extensive and longer clinical trials will be required to determine the safety and effectiveness of the neonatal stem cell medical procedures. New approaches, such as bioengineered scaffolds, AI-driven personalization, and gene-edited stem cells, should be considered to boost the therapeutic practices. It is necessary for ethical and legal rules and regulations to be developed in connection with new neonatal technologies.

Finally, coordinated and very focused efforts should be made to bring stem cell therapy research investment and benefits to improve neonatal health both in the developed and developing countries. Thus, creating a culture of collaboration, diversity, and ethical responsibility would take the field to the level where it could deliver on its promise of improving care for neonates all over the world.



Ethics Committee Approval	Since this research work deals with a study based on a review of existing academic literature, there is no infringement of the rules in the treatment of human or animal subjects. However, the research maintains the citations of the works cited to ensure that full academic standards are met.
Informed Consent	Not applicable.
Peer Review	Externally peer-reviewed.

Author Contributions	Conception/Design of Study- M.T.A.; Data Acquisition- M.T.A.; Data Analysis/Interpretation- M.T.A., H.T.Ç.; Drafting Manuscript- M.T.A.; Critical Revision of Manuscript- M.T.A., H.T.Ç.; Final Approval and Accountability- M.T.A., H.T.Ç.
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 22.01.2024
Accepted: 24.03.2025

Case Report

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Double Aortic Arch And Ventricular Septal Defect With Pulmonary Atresia: A Rare Combination In A Congenital Heart Surgery



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Abstract

Rare combinations of congenital heart pathologies can make the management of the surgical repair difficult and may complicate the procedure. We would introduce a newborn diagnosed with ventricular septal defect, pulmonary atresia and double aortic arch and the successful palliative surgery with shunt procedure of the patient. Atypical ductus, double aortic arch and the different configuration of its branches can complicate the usual shunt procedure. Variations in vascular structures may be the reason for complications in congenital heart surgery. Before planning the surgical procedure, vascular anatomy should be presented in detail even for palliative operations. Blalock-Taussig shunt can be performed safely in the case of a double aortic arch.

Keywords

Double aortic arch • ventricular septal defect • pulmonary atresia



“ Citation: İştar, H. & Harmandar, B. Double Aortic Arch And Ventricular Septal Defect With Pulmonary Atresia: A Rare Combination In A Congenital Heart Surgery. Çocuk Dergisi–Journal of Child 2025; 25(1): 52-54. DOI: 10.26650/jchild.2025.1424023

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INTRODUCTION

Double aortic arch is a variation that occurs due to the persistence of both aortic arches in uterine life [1]. Septal defects, tetralogy of Fallot, transposition of the great arteries, heterotaxy/asplenia syndrome, dextrocardia, right ventricular-dominant atrioventricular canal defect, and double-outlet right ventricle association can be seen in the same individual [1]. We introduce a case report of a pediatric patient diagnosed with double aortic arch, ventricular septal defect, and pulmonary atresia.

CASE REPORT

A 12-day-old and 3 kg in weight term newborn was examined by echocardiography due to the cyanosis with oxygen saturation 80% in room air. On computed tomography angiography, the patient was diagnosed with pulmonary atresia (PA), ventricular septal defect (VSD), and double aortic arch (Figure 1A, 1B, 1C, 1D). The right arch was larger. Its course was through the right side of the vertebral column. On parallel, the left arch was smaller, and the arch branches and ductus arteriosus originated from the left arch. We did not find any sign of compression on the trachea. Because of the PA and severe cyanosis, we decided to perform a shunt operation. Written informed consent for publication was obtained from the patient's relatives. Permission strong[was granted by the patient's relatives to publish the case report.

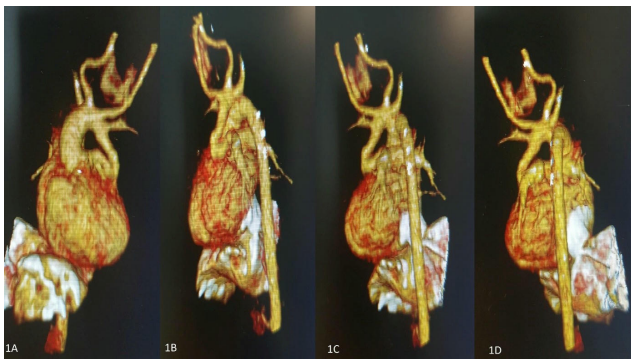


Figure 1. a, b, c, d. Preoperative views of the double aortic arch on computed tomography.

Median sternotomy was performed for better exploration. After complete dissection, the presence of a double arch and ductus arteriosus was confirmed (Figure 2A). For identifying both subclavian arteries, we introduced right and left radial artery catheters previously and a temporary occlusion test was performed for each branch intraoperatively. The ductus arteriosus was connecting the pulmonary confluence to the distal part of the descending aorta. The ductus arteriosus had a tortuous and dilated form and was severely narrowing at the connection of the pulmonary confluence (Figure 2B, 2C,

2D). After a heparin dose of 1 mg/kg was administered, a polytetrafluoroethylene (PTFE) graft of 4 mm was interposed between the right pulmonary artery and the proximal part of the right subclavian artery with an 8/0 polypropylene suture (Figure 3A). When adequate blood supply was obtained through the modified Blalock-Taussig shunt, division of the ductal tissue was performed. The narrowing on the left pulmonary artery was enlarged with a PTFE patch (Figure 3B). Dissection around the aorta was performed and adequate mobility was provided to prevent any compression on the trachea caused by the previous vascular ring effect. Postoperative 2nd day patient tolerated the extubation and acetylsalicylic acid was began 6 mg/kg once a day. On the 7th day after the operation, the patient was discharged without any problem in use only acetylsalicylic acid.

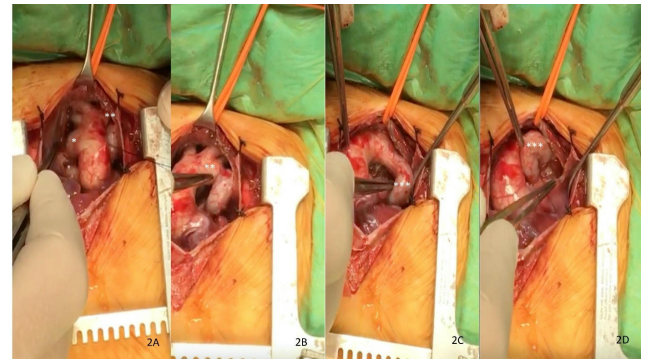


Figure 2. a. Left and right (marked with) aortic arches with branches originating from the left aortic arch. **b.** Left aortic arch (marked with). **c.** Elongated and dilated PDA (marked with).

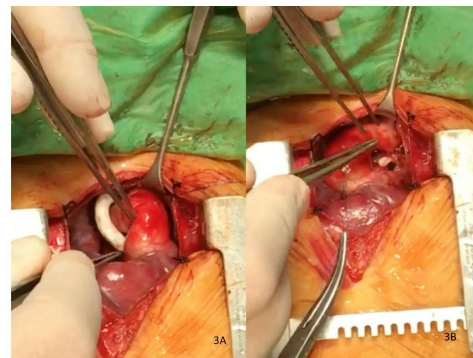


Figure 3. a. Right modified Blalock-Taussig shunt. **b.** Enlargement of the left pulmonary artery using a PTFE graft.

DISCUSSION

The double aortic arch may include archs with the same diameter, or one of them may be hypoplastic. The right arch is frequently dominant [2]. Branches arising from arch (ie truncus arteriosus, carotid arteries) can be arranged in various manners. The double aortic arch produces a vascular ring around the esophagus and trachea. For isolated double arch,

infants present with respiratory stridor or dysphagia in the early years of their life [2]. The double aortic arch is associated with the tetralogy of Fallot [3], atrioventricular canal defect [1], coarctation of the aorta [1], VSD and pulmonary stenosis [4], or VSD-PA association [5]. Our aim was to determine the appropriate subclavian artery for the shunt procedure with an appropriate angle and to provide adequate mobility for preventing the compression on the trachea. The arrangement of branches on the double aortic arch should be checked with computed tomography in case of complex intracardiac disease.



Peer Review Externally peer-reviewed.

Author Conception/Design of Study- H.İ.; Data Acquisition-

Contributions H.İ.; Data Analysis/Interpretation- B.H.; Drafting Manuscript- H.İ.; Critical Revision of Manuscript- B.H.; Final Approval and Accountability- B.H., H.İ.

Conflict of Interest Authors declared no conflict of interest.

Financial Disclosure Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Submitted: 27.10.2024
Revision Requested: 17.12.2024
Last Revision Received: 25.12.2024
Accepted: 27.12.2024

Case Report

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Iatrogenic Esophageal Perforation in Extremely Preterm Infants: A Report of Three Cases



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Abstract

Iatrogenic esophageal perforation in neonates is a rare but serious complication that can occur during medical interventions. Early diagnosis and intervention are of vital importance. In recent years, surgical treatment has been replaced by conservative approaches. In this article, three cases of esophageal perforation that developed during the insertion of an orogastric (O/G) tube are presented.

Keywords

Esophagus • neonate • perforation



“ Citation: Adak, A. M., Durak, F., Kara, M. B., İsbir, C., Orman, A. & Çelik, Y. Iatrogenic Esophageal Perforation in Extremely Preterm Infants: A Report of Three Cases. Çocuk Dergisi–Journal of Child 2025; 25(1): 55–59. DOI: 10.26650/jchild.2025.1573234

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INTRODUCTION

Iatrogenic esophageal perforation in neonates is a rare but potentially fatal complication that can occur during medical interventions such as orogastric tube (O/G) or nasogastric (N/G) tube insertion and endotracheal intubation and has an incidence of 0.4-0.5%¹⁻³. This rate is approximately 10 times higher in extremely low birth weight babies^{1,2}. Iatrogenic esophageal perforation may lead to mediastinitis, sepsis, respiratory failure, hemodynamic instability, and even death. Clinical outcome is directly related to the time between perforation and treatment⁴. Mortality rates of up to %20-30 have been reported in esophageal perforation in neonates, but death is mostly associated with comorbidities of prematurity rather than esophageal perforation⁵⁻⁷. Although conservative treatment methods such as discontinuation of enteral feeding, antibiotics, and total parenteral nutrition (TPN) are successful in selected patients, surgical procedures are rarely required in cases of clinical deterioration despite conservative treatment⁸.

In this report, we present three cases of iatrogenic esophageal perforation, one of which was referred from an external center and the other two developed iatrogenic esophageal perforation during hospitalization in our hospital.

CASE 1

The baby girl, who was born at 27 gestational weeks (GW) by emergency cesarean section at an outside center with a weight of 775 g due to preeclampsia as the 3rd living baby from the 5th pregnancy of a 29-year-old mother, was transferred to our hospital on the 8th day of her life intubated with a diagnosis of pneumothorax in the right lung and suspicion of esophageal perforation. She was followed up in the HFOV mode. The right-sided course of O/G was observed on X-ray radiography, and esophageal perforation was considered (Figure 1). The patient was referred to the pediatric surgery department, and the N/G tube was inserted under scopic guidance. Enteral feeding was discontinued, and TPN and broad-spectrum antibiotic (vancomycin, meropenem, fluconazole) treatment were started. In the follow-up, minimal enteral nutrition with the N/G tube was started on the 21st day of hospitalization and the thoracic tube was removed on the 48th day of hospitalization. During the follow-up of the patient who was followed up with the pediatric surgery department, feeding was gradually increased and full enteral feeding was started on the 90th day of hospitalization. The patient who received invasive mechanical ventilation support for 84 days and noninvasive mechanical ventilation support for 88 days in total received systemic steroid treatment in accordance with the DART protocol due to bronchopulmonary dysplasia. The

patient, who was in good general condition, breathing room air and fed completely orally, was discharged with healing on the 194th postnatal day after the completion of follow-up and treatment.



Figure 1. Right-sided course of the orogastric tube (indicated by arrow)

CASE 2

A male infant born via cesarean section at 26 GW, weighing 1016 g, as the second living twin from a 21-year-old mother's first pregnancy, was admitted to the NICU with nasal CPAP applied in the delivery room. Ampicillin, gentamicin therapies, and fluconazole prophylaxis were initiated. The patient, who had a high oxygen requirement, received surfactant via the minimally invasive surfactant treatment (MIST) method due to respiratory distress syndrome and was monitored on non-invasive positive pressure ventilation (NIPPV). On the third day of his life, a chest tube was inserted due to right pneumothorax, a liquid fluid was obtained from the pleural cavity suggestive of nutritional content and the course of the O/G tube was seen to be toward the right lung instead of the stomach on the X-ray, and esophageal perforation was considered (Figure 2). The patient was consulted with the pediatric surgery department, enteral feeding was discontinued, an N/G tube was placed under fluoroscopy guidance on the postnatal 3rd day, and TPN along with broad-spectrum antibiotic therapy was initiated. The patient, who experienced increased oxygen needs and developed carbon dioxide retention, was intubated and monitored in the SIMV + VG + PSV (Synchronized Intermittent Mandatory Ventilation + Volume-Guaranteed Ventilation + Pressure Support Ventilation) mode. On the 19th day of life, enteral feeding was continued under the supervision of pediatric surgery, but septic shock developed on the 25th day of life before complete enteral feeding could be started during

follow-up, and the patient died on the 27th postnatal day due to late-onset neonatal sepsis.

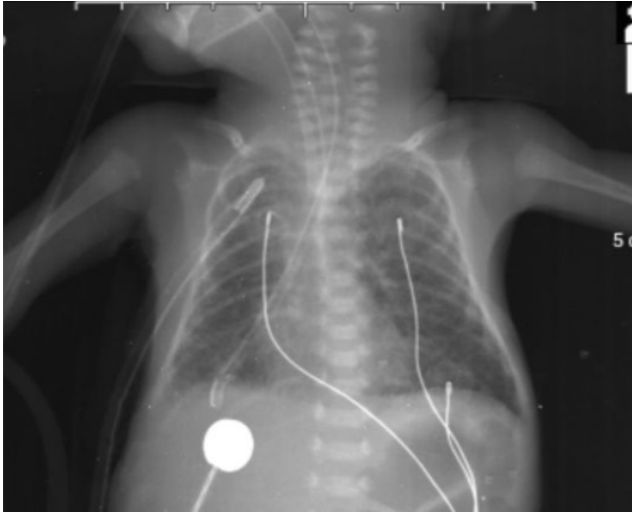


Figure 2. The orogastric tube was seen to be toward the right lung instead of the stomach (indicated by arrow)

CASE 3

A female infant born at 27 GW, weighing 1050 g, as the first living twin from a 29-year-old mother's first pregnancy, was admitted to the NICU with nasal CPAP applied in the delivery room due to preterm labor. Ampicillin, gentamicin therapies, and fluconazole prophylaxis were initiated. The patient, who had a high oxygen requirement, received surfactant via the MIST method because of respiratory distress syndrome and was monitored on non-invasive positive pressure ventilation (NIPPV). On the second day of life, the patient who continued to have respiratory distress and developed carbon dioxide retention was intubated and followed up with respiratory support in the HFOV mode. On the fourth day of life, posteroanterior and lateral chest X-rays revealed a radiolucent area in the posterior cardiac region (Figure 3 and 4). The patient was consulted with the pediatric surgery department because of the suspicion of Morgagni hernia or esophageal perforation. Thoracic computed tomography showed a limited focal air density in the mediastinum, and it was observed that there was an esophageal perforation limited to the mediastinum (Figure 5). With a conservative approach, enteral feeding was discontinued, and TPN along with broad-spectrum antibiotic therapy was initiated. During follow-up, the patient, whose ventilator parameters were minimal in the HFOV mode and blood gas monitoring was normal, was switched to the conventional mode (SIMV + VG + PSV). The patient was followed up in collaboration with the pediatric surgery department, and minimal enteral nutrition was started on the 16th day and gradually increased, and full

enteral nutrition was started on the 34th day. The patient, who received 38 days of invasive and 27 days of non-invasive mechanical ventilation support, was treated with systemic steroids for bronchopulmonary dysplasia. After completing the follow-up and treatment, the patient, who was in good general condition, breathing room air, and fully orally fed, was discharged with full recovery.



Figure 3. A radiolucent area in the posterior cardiac region (indicated by arrow)



Figure 4. A radiolucent area in the posterior cardiac (indicated by arrow)



Figure 5. A limited focal air density in the mediastinum (indicated by arrow)

DISCUSSION

Iatrogenic esophageal perforation can be a rare complication of procedures frequently performed in neonatal intensive care units, such as endotracheal intubation, O/G, or N/G tube placement⁹. The most common anatomical site of perforation is the thoracic esophagus, followed by the cervical esophagus¹⁰. Iatrogenic cervical esophageal perforations can occur, particularly when multiple attempts are required during difficult intubation. This is due to factors such as neck hyperextension during the procedure, stretching of the cricopharyngeal muscle, and the esophageal wall being stretched toward the cervical vertebrae, making the esophagus more susceptible to damage¹¹. Thoracic esophageal perforations are mostly caused by the insertion of O/G or N/G tubes, and their occurrence can be related to the characteristics of the tube, with a higher frequency noted in polyvinyl tubes¹⁰. This complication is more common in extremely preterm and very low birth weight infants^{12–14}. Esophageal perforation can present in three forms: as a pseudodiverticulum, as a mucosal perforation with limited extravasation extending posteriorly into a blind-ending submucosal area, and as a full-thickness esophageal perforation with air or esophageal contents freely leaking into the intrapleural space^{13,14}. Although the usual routes of perforation are into the mediastinal, pleural, and peritoneal spaces, there are reports in the literature, albeit rarer, of N/G or O/G tubes penetrating into other organs, including the pericardial sac¹⁵, renal pelvis¹⁶, and bladder¹⁷. Proximal esophageal perforation typically presents

findings and radiological abnormalities on the left side of the lung radiograph, whereas distal perforation manifests findings and abnormalities on the right side^{1,18,19}. In all three of our cases, a right-sided distal esophageal perforation occurred, believed to have occurred during the placement of the N/G tube, resulting in two cases of complicated perforation causing pleural injury and one case of isolated full-thickness perforation confined to the mediastinum. In the past, iatrogenic esophageal perforation in neonates was mostly treated surgically, similar to that in older children and adults. However, in recent years, conservative treatment has gained importance^{4,5,12,13,20}. Although it is a complication with high mortality and morbidity, these rates are associated with the time interval between the occurrence of the perforation and the diagnosis^{12,19}. In all three of our cases, a retrospective review of the direct radiographs confirmed the diagnosis of esophageal perforation within hours. The conservative treatment option was chosen, and enteral feeding was discontinued, while total parenteral nutrition and broad-spectrum antibiotics were initiated. Two of our cases were discharged in good health, while the third, despite the perforation healing and enteral feeding being resumed, succumbed to respiratory failure and late-onset neonatal sepsis due to the presence of additional comorbidities. As in our cases, in a multicenter study involving eight premature infants in Europe, eight premature infants with esophageal perforation were treated conservatively and one of them died, but the cause of death was not perforation; it was attributed to complications related to prematurity⁹.

CONCLUSION

Early diagnosis and intervention are crucial in iatrogenic esophageal perforation, a rare complication that can develop during medical procedures performed in neonatal intensive care units. Even a 24-h delay in diagnosis can nearly double the mortality rate³. Therefore, it is essential for healthcare professionals to be aware of the signs associated with iatrogenic esophageal perforation and the management strategies to either prevent this condition or address it promptly.



Peer Review	Externally peer-reviewed.
Author	Conception/Design of Study- Y.Ç., A.O., A.M.A.; Data
Contributions	Acquisition-A.M.A., M.B.K., F.D. ; Data Analysis/ Interpretation- A.M.A., M.B.K., F.D., C.İ.; Drafting Manuscript- A.M.A., M.B.K.; Critical Revision of Manuscript- Y.Ç., A.O., C.İ., A.M.A.; Final Approval and Accountability- Y.Ç., A.O., C.İ., A.M.A., F.D., M.B.K.
Conflict of Interest	Authors declared no conflict of interest.
Financial Disclosure	Authors declared no financial support.



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Çocuk Dergisi Journal of Child

Submitted: 29.12.2024
Revision Requested: 23.01.2025
Last Revision Received: 03.02.2025
Accepted: 04.02.2025

Review Article

Open Access

Development of Child Health in the Republic of Türkiye: A Century, From Tradition to the Future



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Abstract

In the 100th anniversary of our Republic, we have reviewed the developments in child health led by Gazi Mustafa Kemal Atatürk and his comrades and improved by esteemed professors. The impact of the topics in the National Turkish Medical Congresses held between 1925 and 1986 is reflected until today. We included information on social and education rights, nutritional problems, breastfeeding, and vaccination of children around the world and in Türkiye. With demographic data in the 100th Year of the Republic, we examined the crude birth rate, mortality, and dependency rates. We have endeavored to address the situations that await us in the future in terms of chronic diseases, media addiction, vaccine hesitancy/refusal, and the digital world and biotechnology, which now occupy a big place in our lives.

Keywords

Child Health • 100th anniversary • Republic of Türkiye



“ Citation: Bakır Kayı, A., Keskindemirci, G., Özbörü Aşkan, Ö. & Gökçay, E. G. Development of child health in the republic of Türkiye: a century, from tradition to the future. Çocuk Dergisi–Journal of Child 2025; 25(1): 60-67. DOI: 10.26650/jchild.2025.1608583

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Introduction

Based on the philosophy of the Republic era, "Turk, Glory, Work, Trust Yourself" we aimed to compile the achievements in the field of child health attained over the past century of the Republic, with the invaluable contributions of all our esteemed scholars. As we commemorate with love, respect, and gratitude all our predecessors, foremost among them Gazi Mustafa Kemal Atatürk and his comrades who founded and advanced our Republic to this day, we also sought to address the necessities of the new century, enriched by the experiences and knowledge accumulated over the years.

Clinical and Research Consequences

Achievements in Child Health in the Republican Era

Approximately two years after the proclamation of the Republic of Türkiye, on September 1, 1925, the National Turkish Medical Congress was inaugurated with the participation of President Gazi Mustafa Kemal Atatürk and a speech by Prime Minister İsmet İnönü. In his opening speech, İsmet İnönü said, "If in a country, scholars, authorized scientists, transfer their knowledge to all classes of society and are effective and useful, that country will develop" (1).

One of the main topics of the First National Turkish Medical Congress was child mortality, with an emphasis on improving prenatal, birth, and postnatal mortality and care. Many issues were addressed, including the importance of breastfeeding, social assistance for school children, the reports of the institutions for the protection of children, the importance of having documents to identify child mortality, and the training of statistical experts (Table 1) (1).

The Geneva Declaration of the Rights of the Child, adopted by the League of Nations in 1924, was signed by Atatürk himself in 1931 and adopted by the Republic of Türkiye (2). Atatürk, who found love, life, and vitality in the word "child", called his loved ones children, regardless of their age, and presented National Sovereignty and Children's Day to children on April 23, 1929 (3). The Convention on the Rights of the Child adopted by the United Nations in 1989 was signed by Türkiye in 1990 and put into force (3). The importance of children's rights, birth, death, disease, nutrition and housing data, and the social and sensory development of children is increasing day by day.

Social Rights and Education

Considering the declarations on the rights of the child, the rights of Turkish children were determined and presented to the public in order to address an issue that was of close

Table 1. Main topics of the National Turkish Medical Congresses (1923-1968)

Congresses	Year	Main Topic(s)*
1 st National Medical Congress	1925	Child mortality, malaria, and surgical tuberculosis
2 nd National Medical Congress	1927	Trachoma, tuberculosis
3 rd National Medical Congress	1929	Syphilis, cancer, scarlet fever
4 th National Medical Congress	1931	Rachitis, nutrition in the city and village
5 th National Medical Congress	1933	Intestinal parasites, spa, mineral waters, drinking
6 th National Medical Congress	1935	Toxicomania, rheumatism
7 th National Medical Congress	1938	Eugenics, influenza
8 th National Medical Congress	1943	Sports medicine, gallbladder diseases
9 th National Medical Congress	1946	Village health, vitamins
10 th National Medical Congress	1948	Occupational medicine, thyroid diseases
11 th National Medical Congress	1950	Tuberculosis
12 th National Medical Congress	1952	Child Health, rheumatism
13 th National Medical Congress	1954	Allergy, physician-state, physician-community
14 th National Medical Congress	1956	Atherosclerosis and the social status of Turkish physicians
15 th National Medical Congress	1958	Lung cancer, Cardiac Surgery, Türkiye's health plan
16 th National Medical Congress	1960	Water and electrolyte disorders, rehabilitation
17 th National Medical Congress	1962	Psychosomatic medicine, Leprosy, Public health/Medical specialization
18 th National Medical Congress	1964	Hypertension/poliomyelitis, medical residency/traffic accidents
19 th National Medical Congress	1966	Cancer, population and family planning, geriatric
20 th National Medical Congress	1968	Shock, fertility and sterility, and medical legislation in Türkiye

* Original papers on different topics were also presented and discussed at each congress.



interest to Atatürk. Among the articles, the right to education stands out and was summarized as the right to good care, to receive attention, love and help everywhere, to rescue a child in distress, that no child should be prevented from formal education before the age of sixteen, that no child should be made to work, that administrative authorities, mayors, mukhtars and national education administrations should be held responsible along with parents, and that the treatment of sick children should not be interrupted (2).

In addition, children's social rights are universally protected through global action plans. The World Health Organization (WHO) has achieved significant progress with the Framework Convention on Tobacco Control (2005) as a global action plan. Furthermore, since 2008, it has provided guidance, agreements, and policy reports on mental health; since 2010, on physical activity; and since 2014, on sugar intake and childhood obesity (4). In Türkiye, numerous studies have been conducted on school-aged children in line with these policies.

Demographic Data in the 100th Year of the Republic

The age structure of Türkiye's population is changing

In 2023, the population pyramid of 1935 has turned into a cylindrical structure; it can be said that the population is getting older with a decrease in the child population and an increase in the elderly population (Figure 1). The proportion of the elderly (65+) population, which was 3.9% in 1935, was 10.2% in 2023, and according to population projections, this proportion is projected to be 25.6% in 2080. The ratio of the elderly population to the total population exceeding 10% is an indicator of population aging (5).

The child population, including the 0-17 age group, constituted 48.5% of the population in 1970, 41.8% in 1990 and 26% in 2023. Türkiye has a rate of 26%, which was above the average child population of the European Union (EU) member countries (18%) (6).

In 2023, while the total dependency ratio was 46.3%, the dependency ratio for children (0-14) was 31.4% and the dependency ratio for the elderly (65+) was 15%. For 2080,

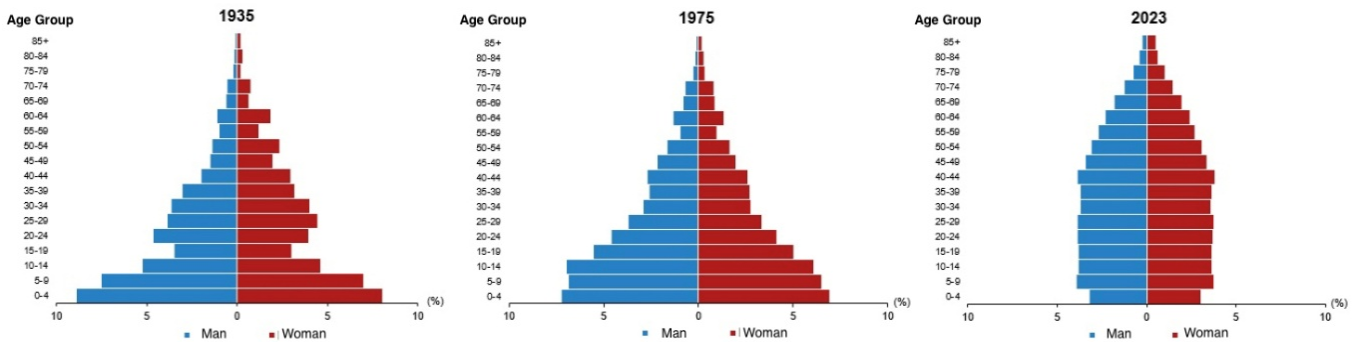


Figure 1. Türkiye population pyramid 1935, 1975 and 2023 (5)

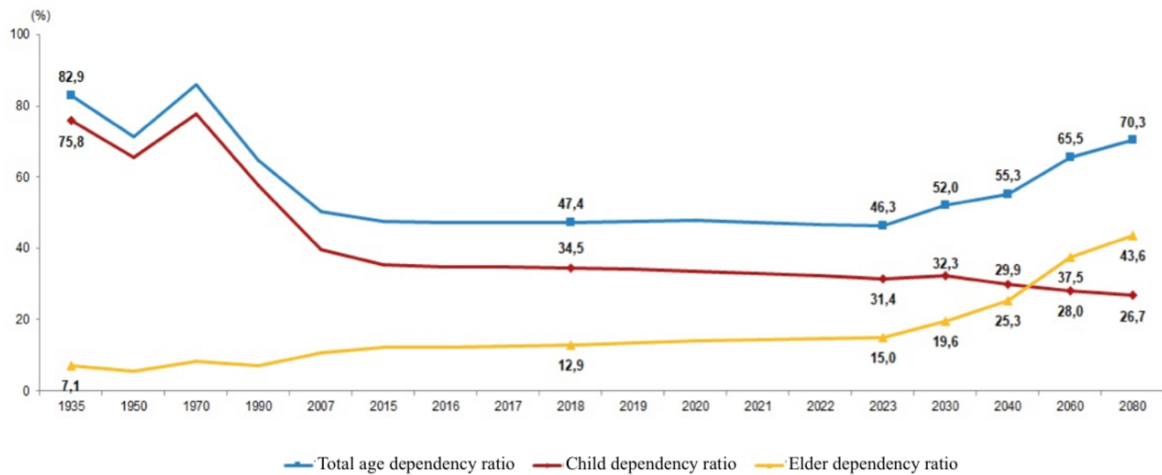


Figure 2. Total, child, and elderly dependency rates in Türkiye between 1935 and 2080 (6)

these rates were estimated to be 70.3%, 26.7%, and 43.6%, respectively (Figure 2) (6).

It was observed that the total fertility rate for Türkiye decreased from 2.38 in 2001 to 1.51 in 2023. With a total fertility rate of 1.63 per thousand in 2022, Türkiye ranked 5th among the European Union member countries (7).

When the crude birth rates of 27 European Union member countries were analyzed, it was observed that the average for 2022 was 8.7, and the highest crude birth rate was 12.0 per thousand in 2021 (7, 8). The World Health Organization estimated the crude birth rate for Türkiye to be 50.01 in 1950, 14.79 in 2023 and 8.49 in 2099 (Figure 3) (9).

According to population projections, the child population ratio in Türkiye was projected to be 25.6% in 2030, 23.3% in 2040, 20.4% in 2060 and 19.0% in 2080 (Figure 4) (6).

A measure of health: mortality

As understood from the results and action plans of the First National Turkish Medical Congress, the recording of deaths is an important tool for the assessment of Turkish public health. In terms of child health and development, the infant mortality rate and the under-five mortality rate are valuable child health indicators. In 2022, the number of live-born babies was 1,035,795, and the number of infant deaths was 9,522 (8, 10).

In 1953, around 200 infants per 1000 live births died before reaching the age of one, while 74 infants died in 1990, 38 in

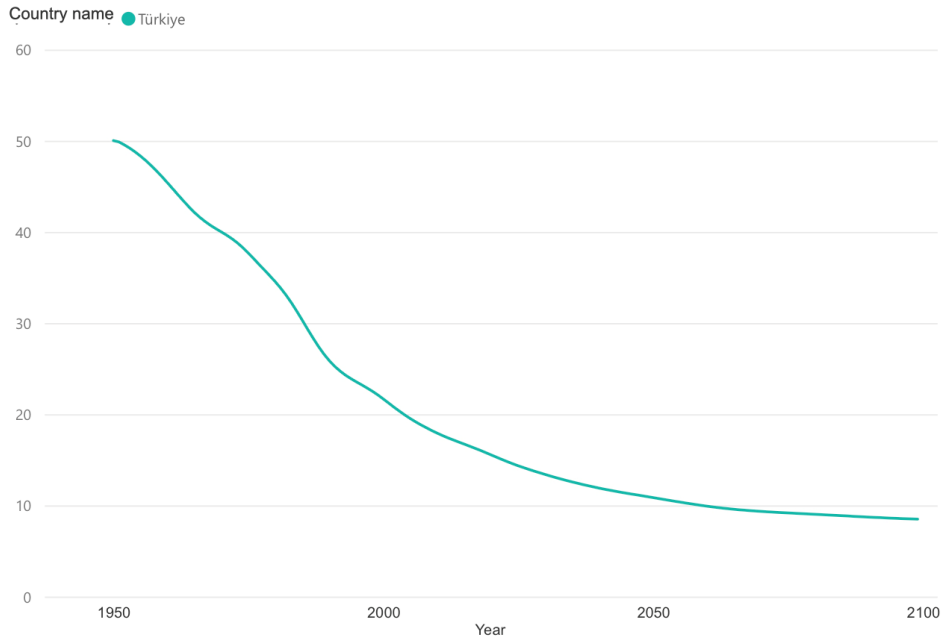


Figure 3. Crude birth rate in Türkiye between 1950 and 2099 (9)

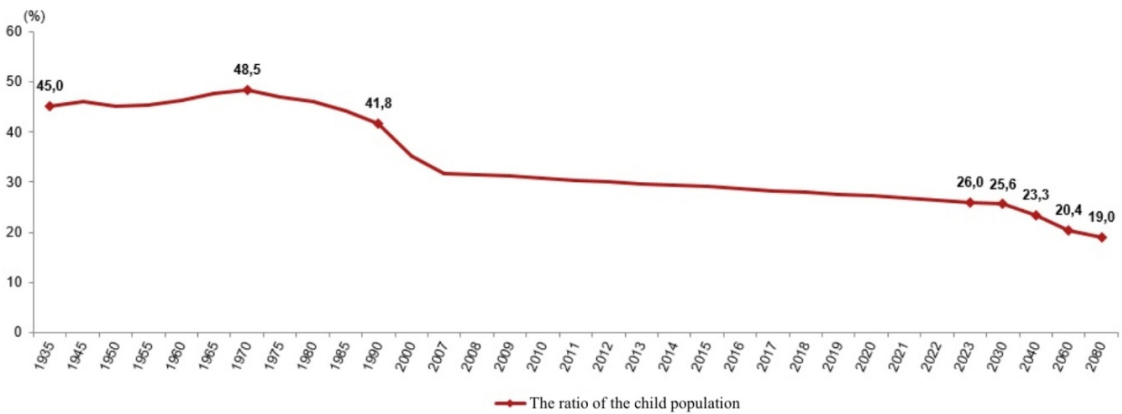


Figure 4. The ratio of the child population to the total population, 1935-2080 (6)

2000 and 9.1 in 2022. This rate was calculated as 28.4% in the world, 4.9% in high-income countries and 3.1% in the EU (11, 12, 13). The most important factors affecting the infant mortality rate have been determined as prenatal care, childbirth care and maternal education level (14).

While the under-five mortality rate was around 300 per 1000 live births in 1953, it changed positively to 11.1 in 2022. This rate was calculated as 38.1% in the world, 5.7% for high-income group countries and 3.7% for the EU (11, 12, 13).

Nutritional problems in children and developments over the years

Stunting prevalence (height-for-age <-2 SD) among children 0-5 years of age, which was given as 23.6% in 1993, decreased over the years and was calculated as 6% in 2018. According to UNICEF's world report for 2023, Türkiye's stunting prevalence for 2022 was reported to be at a low level (2.5% - <10) with 5.5% (15, 16).

The underweight (weight-for-height <-2 SD) rate for children aged 0-5 years, which was 3.9% in 1993, was 1.7% in 2018 and was reported to be at a very low level (<2.5 %) with 1.7% according to the UNICEF's world report for 2023 (15, 16).

The rate of overweight (weight for height $> +2$ SD), which was given as 4.9% in 1993 for children aged 0-5 years, was given as 8.1% for 2018 and it was reported to be at an intermediate level (5% - <10 %) with 8.1% in Türkiye according to UNICEF's world report for 2023 (15, 16).

It was reported that obesity in school children in Türkiye was 10.2 times higher in 2011-2015 compared to 1990-1995, and this rate was 26.3 for boys and 6.2 for girls (17). According to the data from the Childhood Obesity Survey of Türkiye - COSI-TUR 2016, the BMI z-score groups of the anthropometrically measured children (primary school 2nd grade students) are distributed as underweight (z-score <-2) 1.5%, normal ($-2 < \text{z-score} < 1$) 74%, overweight ($1.01 < \text{z-score} < 2$) 14.6% and obese (z-score > 2) 9.9% (18).

Breastfeeding

In our country, improvements in maternity leave for white-collar workers in 2011 ensured the protection and dissemination of breastfeeding. Regulations are felt more effectively with the breastfeeding advocacy of female physicians who benefit from breastfeeding rights (19). According to the results of the Türkiye Demographic and Health Surveys, the rate of breastfed children was 95.2% in 1993, 95.2% in 1998, 96.8% in 2003, 96.7% in 2008, 96.4% in 2013 and 97.8% in 2018. The proportion of infants younger than 6 months receiving exclusively breastfed was calculated as

10.4%, 10.7%, 20.8%, 41.6%, 30.1% and 40.7%, respectively. This steady and rapid increase was considered to be a successful outcome of the initiatives aimed at protecting and promoting breastfeeding (20).

With the right information, education, and support, there are mothers who can breastfeed their adopted child in a period suitable for breastfeeding (21). The World Health Organization supports the miraculous way of feeding, which is the gold standard in every aspect (22).

Vaccine developments

The Expanded Programme on Immunization (EPI), which was initiated by the World Health Organization to prevent deaths from vaccine-preventable diseases, was put into practice in our country and vaccination rates showed a significant increase from 1980 to 2022 (23, 24). According to the WHO's 2023 report, the number of zero-dose/never vaccinated and incomplete DTP vaccinated children globally was 14.3 million in 2022, 18.1 million in 2021 and 12.9 million in 2019 (25). Vaccination rates in Turkey in 2022; Bacillus Calmette-Guérin (BCG) 98%, Diphtheria-Tetanus-Pertussis (DTP)1 99%, DTP3 99%, Hepatitis B (HEPB)3 99%, HEPBB 99%, Haemophilus influenzae type B (HIB)3 99%, Inactivated polio vaccine (IPV)1 99%, Pneumococcal conjugate vaccine (PVC)3 95%, and Rubella-containing vaccine (RCV)1 95% (23).

What are the future expectations?

On the 100th anniversary of our Republic, new health-related problems in children are emerging in our country as in the world. The most prominent of these are:

Chronic diseases

Chronic diseases are among the reasons leading to disability in children (26). Chronic diseases and disability can both interrupt the child's education and social life and turn him/her into an adult who cannot reach his/her potential and leave him/her behind from the society. The level of importance of chronic diseases has increased with health and biotechnological advances and the prolongation of life span. The reintegration of children with chronic diseases into society by providing the necessary conditions is being addressed globally.

The World Health Organization (WHO) revised the "International Classification of Functioning (ICF)" in 2007 and published it as the "International Classification of Functioning, Disability and Health for Children and Young People (ICF-CY)" (27). In Türkiye, a regulation was issued for evaluating child-specific special needs (ÇÖZGER-Çocuklar için Özel Gereksinim Raporu) (26).



According to WHO data, the leading chronic (non-communicable) diseases as a cause of Disability-Adjusted Life Years (DALY) between 2000-2019 in Türkiye are; Congenital anomalies since 2000 for 0-1 and 1-4 years, leukemia and congenital anomalies were replaced by asthma for 5-9 years, anxiety disorders for 10-14 years, and depressive disorders for 15-19 years (28, 29). Regional differences, regular data collection, and the adaptation of adult metrics to the pediatric group are among the future topics for synergistic measures like DALY and their management (29, 30).

Media addiction, digital parents

In the 2021 report of the Turkish Statistical Institute, it was stated that the rate of daily and regular internet use increased, the time spent on social media was approximately 3 hours, and 82% of children aged 6-15 years used the internet (31). It has been shown that media use in preschool children goes back to infancy and that the factors affecting media use are the child, parents, and environment (32).

The advancement of technology, the increase in media addiction due to easily accessible media tools and the internet, the more sedentary lifestyles of children, and the accompanying health problems are among today's issues. Along with their physical and mental development, the fact that the child's safety is at risk in an uncontrolled virtual environment is seen as a major problem.

This technological progress has also brought parents to take on the role of "digital parenting". The concept of digital parenting has the sub-dimensions of digital literacy, awareness, control, ethics, and innovation. A parent who acts according to the requirements of the digital age, has a basic command of digital tools, can protect their child in the virtual environment, and can educate their child about technology (33).

Vaccine hesitancy and vaccine refusal

The WHO defines vaccine hesitancy as reluctance or refusal to be vaccinated despite the availability of vaccination (34, 35). The history of vaccine hesitancy dates back to the late 18th century, when Jenner discovered the smallpox vaccine in 1796 (35). When religious beliefs, distrust in medicine, and negative experiences from the environment combine, vaccine hesitancy turns into vaccine refusal.

With the efficacy of the smallpox vaccine, some western countries enacted compulsory vaccination laws toward the end of the 19th century to protect public health, imposing strict penalties in case of non-vaccination (35). Compulsory vaccination policies are perceived as a violation of personal freedoms and lead to legal struggles (36). These struggles

also occurred during the COVID-19 period. Because of misinformation, the measles vaccine was associated with autism and vaccination rates decreased, leading to measles outbreaks again. Furthermore, once again, the damaging effect of misinformation on public health has been clearly revealed (37).

In 2019, the WHO listed vaccine hesitancy among the ten threats to global health. It also underlined that the causes of vaccine hesitancy are complex and that healthcare professionals are the most reliable advisors and influencers in the fight against it and should be supported (34).

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) continues to work in this field, and with the increase in vaccine hesitancy and refusal in our country, a vaccine portal (<https://asi.saglik.gov.tr/asi/>) was established by the Ministry of Health and aimed to provide exact information about vaccines and to expand awareness (38).

Health Digitalization and Biotechnology

With the rapid advancement of technology, the data generated through the devices and applications we frequently use in our daily lives is increasing. With the increase and storage of data in the health sector, digitalization, data analysis, and decision support algorithms that help physicians are being developed. Radiographic images, MRI, CT, ultrasound, nuclear imaging, pathological reports, bedside devices, wearable technology, services applicable at home, online health services, electronic health records, and telemedicine produce the most remarkable scientific studies in the field of health (39).

Three-dimensional (3D) bioprinting and artificial organ studies, which are seen as a great advantage since the rate of tissue and organ donation is low compared to the rate of transplantation, are among the leading research topics in the field of health (40). It is believed that the integration of bioengineering, biomedicine, and clinical medicine will support the development of personalized medicine with artificial organs that can replace existing organs (41). In addition to scientific research and pharmaceutical studies in the field of health, medical device studies and the supervision of the field, where health and biotechnology are intertwined, are among the shining topics.

Healthcare professionals will benefit public health if their awareness and knowledge of biotechnological development increases. Machine learning algorithms, which have started to make significant contributions to decision-making processes in healthcare, are seen as an important support to healthcare professionals as data sets and application areas are developed.



Conclusion

As in the world, we must struggle with the problems that arise in our country by taking public health as a basis, improving preventive child health and primary child health services, intensifying the field of preventive child health in medical education, and informing the society with epidemiological data. The knowledge, experience, and capability we gained in the first 100 years of our Republic will enable us to overcome all problems and design the new century.



Peer Review Externally peer-reviewed.

Author Contributions Contributions: Conception/Design of Study- A.B., G..K, Ö.Ö.A., E.G.G.; Data Acquisition- A.B., G..K, Ö.Ö.A., E.G.G.; Data Analysis/Interpretation- A.B., E.G.G.; Drafting Manuscript- A.B., G..K, Ö.Ö.A., E.G.G.; Critical Revision of Manuscript- A.B., G..K, Ö.Ö.A., E.G.G.; Final Approval and Accountability- A.B., G..K, Ö.Ö.A., E.G.G.

Conflict of Interest Authors declared no conflict of interest.

Financial Disclosure Authors declared no financial support.

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Çocuk Dergisi Journal of Child

Erratum

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Erratum to: Effects of Mouth Breathing on Craniofacial Growth and Oral Health in Children



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Erratum to: Effects of Mouth Breathing on Craniofacial Growth and Oral Health in Children

DOI: [10.26650/jchild.2022.947700](https://doi.org/10.26650/jchild.2022.947700)

Erratum:

The institution information of the authors has been corrected as follows in the article titled 'Effects of Mouth Breathing on Craniofacial Growth and Oral Health in Children' in the 2022/22(2) issue of the Journal of Child.

The correct is:

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