MATERNAL-FETAL MEDICINE

CrossMark

Gestational age and the long-term impact on children's infectious urinary morbidity

Elisheva Padeh[1] · Tamar Wainstock[2] · Eyal Sheiner[3] · Daniella Landau[4] · Asnat Walfisch[3]

Abstract

Purpose Given the negative impact of prematurity on offspring's health, we sought to determine whether different gestational ages at birth impact differently on the prevalence of childhood infectious urinary morbidity in the offspring.

Methods In this population-based cohort analysis, all singleton deliveries occurring between 1991 and 2014 at a single regional tertiary medical center were included. Gestational age upon delivery was sub-divided into early preterm (< 34 weeks), late preterm (34–36 6/7 weeks), early term (37–38 6/7 weeks), full term (39–40 6/7 weeks), late term (41–41 6/7 weeks) and post-term (> 42 weeks). Congenital malformations were excluded. Rates of infectious urinary morbidity-related hospitalizations of offspring up to age 18 years were assessed using a survival curve and a Cox multivariable model.

Results During the study period, 238,620 deliveries met the inclusion criteria. Urinary-related hospitalization ($n = 1395$) rates decreased as gestational age increased, from 1.7% in the early preterm group, 0.9% in the late preterm group, 0.6% in the early-term group and only 0.5% in the full, late and post-term groups ($p > 0.001$; chi-square test for trends). In the Cox model, controlled for maternal age, preterm as well as early-term deliveries exhibited an independent association with pediatric urinary morbidity as compared with full term (early preterm: aHR—3.305, 95% CI 2.4–4.54; late preterm: aHR—1.63, 95% CI 1.33–1.99; early term: aHR—1.26, 95% CI 1.1–1.43, $p = 0.01$).

Conclusions Deliveries occurring at preterm and at early term are independently associated with pediatric urinary morbidity in the offspring. This risk decreases as gestational age advances.

Keywords Full-term pregnancy · Early-term delivery · Long term · Infectious urinary morbidity

---

Elisheva Padeh and Tamar Wainstock are equal contributors and should be considered as first authors.

✉ Elisheva Padeh
eli77w@gmail.com

1 Joyce and Irving Goldman Medical School, Ben-Gurion University of the Negev, Beersheba, Israel

2 Epidemiology and Health Services Evaluation, Ben-Gurion University of the Negev, Beersheba, Israel

3 Department of Obstetrics and Gynecology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beersheba, Israel

4 Department of Neonatology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beersheba, Israel

Introduction

The negative impact of early prematurity (< 34 0/7 weeks' gestation) on offspring's long-term health is well established [1]. Preterm neonates, born prior to 34 weeks of gestation, are at an increased risk for both immediate as well as long-term morbidity [2]. It has been recently recognized that 'near-term' deliveries (34 0/7–36 6/7 weeks' gestation) exhibit a similar pattern of health risks, albeit to a lesser extent. The term "near term" was consequently changed to "late preterm" as a result of accumulating data making it clear that fetal maturation is part of a continuum and that late preterm delivery neonatal outcome appears more similar to that of preterm than it does to that of term deliveries. Similarly, "term" pregnancy, while still being defined from gestational week 37 and on, is now subdivided into "Early term"—week 37 0/7–38 6/7, "Full term"—week 39 0/7–40 6/7, and "Late term"—week 41 0/7–41 6/7 [3] This is consistent with recent studies supporting the notion that even within term deliveries, short- and long- term sequelae

of the offspring differ [4]. For example, early-term infants are at increased risk, during the neonatal period, for respiratory morbidity and even mortality when compared to those born at full term [3]. Short-term morbidity associated with early-term deliveries was also shown to include longer durations of hospital stay following birth, higher emergency department use, and increased rates of re-hospitalization within the first year of life [5]. Apparently, late preterm infants and early-term infants are metabolically and physiologically less mature than full- and late-term born infants [6]. Later in life, these children are at a higher risk of diabetes and obesity-related disorders [7], cardiovascular morbidity [8], respiratory morbidity [9, 10], neurological disorders, developmental delays, and even death [11]. While respiratory and neurological morbidities have already been extensively investigated, other aspects of the long-term health of early-term offspring have not yet been investigated.

Urinary tract infection (UTI) is considered to be one of the most common pediatric infections [12]. Apart from the immediate illness, UTIs may be associated with later permanent renal scarring and dysfunction in children [12, 13]. Children born prematurely and even at early term may have a relatively immature and hence compromised immune system [14]. Their compromised immune system, in turn, could result in a greater vulnerability to infections and specifically infectious urinary morbidity [15]. In this study, we aimed to focus on infectious urinary morbidity during childhood and its possible association with gestational ages at birth.

Materials and methods

In this population-based retrospective cohort analysis, all singleton deliveries occurring between 1991 and 2014 were included. The study was conducted at the single regional tertiary medical center in southern Israel (Soroka University Medical Center—SUMC), the largest birth center in the country. The study is thus based on non-selective population data. The institutional review board (SUMC IRB committee #0438-15-SOR) approved the study.

The primary exposure was gestational age at birth including all gestational age groups: preterm, term and post-term delivery. All groups were defined by the 'defining Term Pregnancy Workup': "Early preterm"—24 0/7–33 6/7 weeks' gestation, "Late preterm"—34 0/7–36 6/7 weeks' gestation, "Early-term"—37 0/7–38 6/7 weeks' gestation, "Full term"—39 0/7–40 6/7 weeks' gestation, and "Late term"—41 0/7–41 6/7 weeks' gestation and "post-term"—$\geq$ 42 weeks' gestation [3]. Gestational age was based on the best obstetrical estimate determined by healthcare providers and used for clinical decision making. The standard criteria used involved the earliest ultrasound finding while taking the clinical history into consideration. If the last menstrual period (LMP) was certain and consistent with

the ultrasound, dating was based on LMP. If the LMP was unknown, or was not consistent with the ultrasound findings, the ultrasound data were used to determine the gestational age. In Israel, medical services, including prenatal care, are free of charge. Most women therefore complete their first trimester ultrasound visit, enabling physicians to precisely date their pregnancy. As a result, gestational age is very accurate.

We excluded multiple pregnancies, fetuses with congenital malformations, pregnancies with missing gestational age, and perinatal mortality cases (intrauterine fetal death, intrapartum death, and post-partum death). Outcomes assessed included infectious urinary morbidity-related hospitalizations in the offspring up to the age of 18 years. Urinary infectious morbidity was pre-defined in a list of ICD-9 codes detailed in the Supplement Table. At SUMC, the decision of whom to hospitalize with urinary infectious morbidity is based on several clinical factors. The child's age is a major determinant and neonates and young infants with high fever are always admitted. Otherwise, the decision to admit a child for hospitalization is based on clinical judgment.

Follow-up time was defined as time to an event (infectious urinary-related hospitalization), with only the first hospitalization for each child being included, or until censored. Censoring was defined by death (during hospitalization, other than urinary related), or when the child reached the age of 18 years (calculated based on the date of birth).

Data were collected from two databases that were cross-linked and merged: the computerized hospitalization database of SUMC ("Demog-ICD9"), and the computerized perinatal database of the obstetrics and gynecology department at SUMC. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations in any of the SUMC departments including the pediatric division. The perinatal database consists of information recorded immediately following delivery by an obstetrician. Experienced medical secretaries routinely review the information prior to entering it into the database to insure its maximal accuracy and completeness. Coding is performed after assessing medical prenatal care records as well as routine hospital documents.

Statistical analysis

Statistical analysis was performed using the SPSS package 23rd edition. (IBM/SPSS, Chicago, IL). Quantitative normally distributed variables were compared by analysis of variance (Anova), and categorical variables were compared using the Chi square test. Kaplan–Meier survival curves were used to compare cumulative infectious urinary-related hospitalization incidences over time according to gestational age at birth, divided into the six subcategories of gestational ages as detailed above. The differences between the six cumulative morbidity curves (based on the different

gestational age groups) were assessed using the log-rank test.

A Cox hazards model was used to establish an independent association between gestational age at birth and pediatric infectious urinary-related hospitalization risk while controlling for time to event and maternal age as well as several other obstetrical factors. Deliveries occurring at full term were considered as reference. All analyses were two sided, and a p value of < 0.05 was considered statistically significant.

Results

During the study period, 238,620 preterm and term deliveries at SUMC met the inclusion criteria. Of this cohort, 223,242 (93.5%) were term deliveries and 15,378 (6.4%) were preterm deliveries. Within term deliveries, 53,501 (22.4%) occurred at early term, 122,602 (51.4%) at full term, 37,919 (15.9%) at late term, and 9220 (3.9%) during the post-term period. Table 1 summarizes the maternal characteristics and immediate perinatal outcomes according to the different gestational age groups.

As gestational week progressed, mean birth weight gradually increased and the number of children born with low birth weight decreased. Maternal chronic hypertension, diabetes mellitus, smoking, and infertility treatment rates significantly decreased as gestational age at birth advanced. On the other hand, rates of cesarean delivery did not show a linear trend. Up to full-term deliveries, cesarean delivery rates gradually decreased as gestational age advanced. In late- and post-term gestational age groups, cesarean delivery rates increased once again.

Table 1 Maternal and perinatal data according to gestational age

	Early pre-term < 34 0/7 $n = 2405$	Late preterm 34 0/7–36 6/7 $n = 12,973$	Early term 37 0/7–38 6/7 $n = 53,501$	Full term 39 0/7–40 6/7 $n = 122,602$	Late term 41 0/7–41 6/7 $n = 37,919$	Post-term ≥ 42 0/7 $n = 9220$	p value
Maternal age in years at birth, mean (weeks ± SD)	28.14 ± 6.446	28.16 ± 6.244	28.6 ± 5.996	28.01 ± 5.718	27.99 ± 5.675	28.12 ± 5.77	< 0.001
Primiparity (%)	32.2	28.2	23.6	23.8	23.7	18.2	< 0.001
Grand multi-parity (≥ 5 births, %)	31.1	32.8	31.7	31.1	33.2	44.1	< 0.001
Smoking (%)	1.6	1.5	1.4	1	0.7	0.4	< 0.001
Chronic HTN (%)	17.2	12	7.2	4	2.9	2.9	< 0.001
Obesity (%)	0.8	0.9	1.1	0.9	1.2	1.6	< 0.001
Diabetes mellitus (%)	5.9	7.7	8	4.5	2.3	2.2	< 0.001
Preeclampsia/eclampsia (%)	15.7	9.9	5.4	3.1	2.3	2.1	< 0.001
Apgar < 7 at 1 min (%)	22.7	7.5	3.2	2.6	3.4	5	< 0.001
Apgar < 7 at 5 min (%)	3	0.7	0.3	0.2	0.3	0.4	< 0.001
Mode of delivery (% cesarean delivery)	47.3	28.8	21.8	9.2	9.6	12.6	< 0.001
Newborn gender							
Female	46.1	47.4	47.9	49.5	50.1	49.7	< 0.001
Male	53.9	52.6	52.1	50.5	49.9	50.3	< 0.001
Mean birth weight (g) (SD)	1810.7 (560.24)	2608.61 (463.045)	3052.73 (450.136)	3292.36 (417.664)	3431.57 (411.3)	3488.04 (430.5)	< 0.001
Low birth weight (< 2500 g, %)	91.2	41.2	8.6	2	0.9	0.8	< 0.001
Follow-up time (years) median (range)	8.8 (0.0–18.01)	9.6 (0.0–18.01)	8.9 (0.0–18.01)	9.8 (0.0–18.01)	11.4 (0.0–18.01)	11.9 (0.0–18.01)	–

Table 2 Comparison of selected long-term urinary morbidity in children (up to 18 years old) according to the different gestational age groups[a]

Offspring long-term urinary morbidity	Early pre-term < 34 0/7 n = 2405 (%)	Late preterm 34 0/7–36 6/7 n = 12,973 (%)	Early term 37 0/7–38 6/7 n = 53,501 (%)	Full term 39 0/7–40 6/7 n = 122,602 (%)	Late term 41 0/7–41 6/7 n = 37,919 (%)	Post-term ≥ 42 0/7 n = 9220 (%)
Total urinary hospitalizations (n = 1395)	40 (1.7)	112 (0.9)	346 (0.6)	650 (0.5)	203 (0.5)	44 (0.5)
Hospitalizations involving cystitis (n = 7)	0 (0.0)	0 (0.0)	2 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)
Hospitalizations involving pyelonephritis (n = 107)	1 (0.0)	6 (0.0)	23 (0.0)	49 (0.0)	22 (0.1)	6 (0.1)
Hospitalizations involving other urinary morbidities[b] (n = 1286)	38 (1.6)	103 (0.8)	325 (0.6)	605 (0.5)	179 (0.5)	36 (0.4)

[a]Several children had more than one diagnosis

[b]Hospitalizations involving other urinary morbidities include: UTI, site unspecified, other urethritis, urethral abscess (see supplement table)

The cumulative percent of initial infectious urinary morbidity hospitalizations according to age was as follows: 85% of hospitalizations related to infectious urinary morbidity occurred in children up to age 6 years, the vast majority of which occurred within the first year of life. Fifteen percent occurred from the 6th year of life until age 18.

The long-term infectious urinary-related hospitalizations of the offspring are presented in Table 2. At least one hospitalization related to infectious urinary morbidity up to the age of 18 years occurred in 1395 children (0.58% of the entire cohort). Urinary hospitalization rates decreased as gestational age advanced, from early preterm (1.7%) to

Fig. 1 Kaplan–Meier survival curve demonstrating the cumulative incidence of pediatric urinary-related hospitalizations according to gestational age at delivery
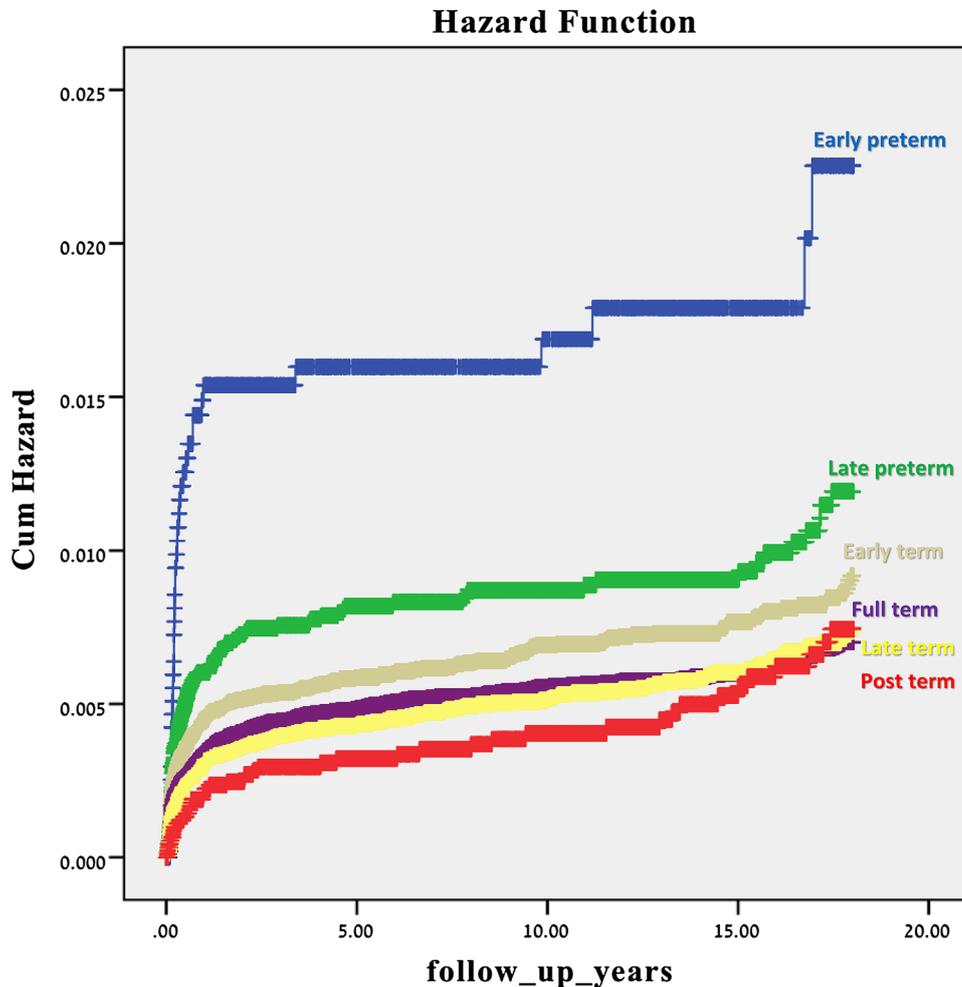
Table 3 Cox hazards regression model for prediction of urinary-related hospitalizations in children (up to the age of 18 years) according to gestational age

Gestational age group	Controlled for maternal age		Controlled for HTN		Controlled for weight		Controlled for induction of labor	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
a. Controlled for length of follow-up								
Full term (39 0/7–40 6/7)	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
Early preterm (< 34 0/7)	3.31	2.4–4.5	3.32	2.4–4.57	2.23	1.53–3.23	3.36	2.44–4.62
Late preterm (34 0/7–36 6/7)	1.63	1.3–1.9	1.65	1.35–2.02	1.37	1.10–1.71	1.64	1.34–2.01
Early term (37 0/7–38 6/7)	1.26	1.1–1.4	1.25	1.1–1.4	1.17	1.03–1.34	1.25	1.1–1.42
Late term (41 0/7–41 6/7)	0.97	0.83–1.13	0.97	0.83–1.13	1.0	0.86–1.18	0.95	0.81–1.12
Post-term (≥ 42)	0.85	0.62–1.15	0.84	0.62–1.15	0.89	0.65–1.21	0.83	0.61–1.12

Gestational age group	Controlled for diabetes		Controlled for cesarean section		Controlled for child birth year	
	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI	Adjusted hazard ratio	95% CI
b. Controlled for length of follow-up						
Full term (39 0/7–40 6/7)	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
Early preterm (< 34 0/7)	3.29	2.39–4.52	3.24	2.34–4.48	3.2	2.33–4.41
Late preterm (34 0/7–36 6/7)	1.64	1.34–2.0	1.63	1.33–1.99	1.66	1.35–2.03
Early term (37 0/7–38 6/7)	1.25	1.1–1.42	1.24	1.09–1.42	1.2	1.05–1.37
Late term (41 0/7–41 6/7)	0.97	0.83–1.14	0.97	0.83–1.14	1.03	0.88–1.21
Post-term (≥ 42)	0.84	0.62–1.15	0.84	0.62–1.15	0.94	0.69–1.28

late preterm (0.9%) to early term (0.6%), but remained stable thereafter: 0.5% in the full, late, and post-term groups ($p = 0.001$; using the Chi square test for trends).

The Kaplan–Meier survival curve (Fig. 1) demonstrated higher cumulative incidence of urinary morbidity in the preterm and early-term groups as compared with later gestational age groups (log rank $p < 0.001$).

Table 3 presents the Cox regression model, controlled for different confounders. Preterm as well as early-term delivery exhibited an independent association with later pediatric infectious urinary morbidity of the offspring as compared to full-term delivery (early preterm delivery aHR—3.3, 95% CI 2.4–4.5; late preterm delivery aHR—1.63, 95% CI 1.3–1.9; early-term delivery aHR—1.26, 95% CI 1.1–1.4, $p = 0.01$). As the number of cases was limited, not all confounders were entered into the same model, and separate models were constructed. We controlled for maternal age, hypertensive disorders, birth weight, induction of labor diabetes, mode of delivery, and year of birth. All models exhibited a similar pattern in which preterm as well as early-term deliveries were found to be independently associated with later pediatric infectious urinary morbidity of the offspring as compared to full-term delivery.

Discussion

In this large population-based cohort study focusing on gestational age upon delivery and later infectious urinary morbidity of the offspring, we found not only preterm deliveries (prior to 37 weeks' gestation) but also early-term deliveries (37–38 6/7 weeks' gestation) to be independently associated with later infectious urinary morbidity of the offspring. This association decreased as gestational age advanced beyond the early-term period and was independent not only of follow-up time, but also of maternal age and morbidity, mode of delivery, and birth weight.

It is now becoming clear that early-term born children may, in general, exhibit similar characteristics to children born preterm in terms of infancy and childhood morbidity, as compared to full- and late-term born children (weeks 39 0/7–42 0/7). Neonates born at early term are not only at increased risk for mortality [3], but also for short- and long-term morbidity. Long-term adverse effects suggested to be more common in early-term born children include respiratory [9, 10], neurological and developmental delays [11], endocrine diseases [7], and cardiovascular morbidity [8].

The increased rates of infectious urinary morbidity presented in the preterm and early-term cohorts may generally be associated with, or even caused by, a relatively immature immune system—more pronounced in preterm born children [14] and possibly early-term children as well.

For preterm infants, one of the reasons for the compromised immune system may be related to intrauterine infection. This infection may lead to either preterm delivery or to early activation of the infants' immune system. Early activation may compromise the infants' immune system by causing immune tolerance, reduced activation of cytokines, and a higher risk of early-onset sepsis. At birth, both the innate and the acquired immune systems are compromised leaving all neonates more susceptible to infections [14, 16]. For preterm babies, this susceptibility to infection may extend into childhood. It is suggested that in preterm infants a lesser developed opsonization system contributes to the greater susceptibility to infection. Other compromised immune defenses such as neutrophil amount and function, antimicrobial proteins and peptides (APP's) as well as complement activity are also not fully developed. Thirdly, a less effective signaling system between the innate and the acquired immune system is also present [15]. During infancy, immune mechanisms gradually mature [14]. As the immune development in early-term babies is best conceived of as on a continuum between that of preterm and full-term infants, all these disrupted mechanisms may exist.

It seems that the innate immune system is the main branch that fights UTIs [17]. As pathogens initially penetrate the barriers of the uroepithelium, they are recognized by Toll-like receptors (TLRs). The TRLs are then activated to recruit a cascade of pro-inflammatory immune responses [18]. The fetal and neonates' immune systems are, however, geared toward a TH2 and TH17 reaction which is anti-inflammatory, while they have a restricted TH1 response which is critical for fighting infection. This anti-inflammatory reaction together with a smaller amount of immune memory cells early in life may explain newborns' high susceptibility to infections [16, 19]. Since most UTIs are caused by uro-pathogenic *E. coli*, TLR4 has a crucial role in recognizing LPS and clearing UTIs [20, 21]. As the expression of TLR4 increases as gestational age increases [22], it is conceivable that the efficacy of TLR4 functioning is on a continuum with gestational weeks. Additionally, decreased expression of MyD88, the adaptor protein of TLR4, may cause a deficient signaling system and hypo-responsiveness to LPS [16]. These assumptions may be particularly true for preterm and early-term neonates placing them at an even higher risk. Until further research determines the pathogeneses of increased infectious urinary morbidity in preterm and early-term born babies, it is conceivable to suggest that

the less well-developed immune system is etiologically central to our findings.

In Israel, preterm birth rates are rather low (approximately, 8%) [23]. This explains the low rates of preterm births observed in our study. In addition, pregnancies with missing gestational age, perinatal mortality cases, and fetuses with congenital malformations were excluded from the study, all of which contribute to the low rates of preterm births observed in the remaining cohort.

Since we found higher rates of maternal chronic hypertension and diabetes in the early-term gestation group, their possible long-term effects on the offspring should be considered. These maternal morbidities may potentially contribute to future development of infections in the offspring or lead to spontaneous or induced preterm or early-term delivery [24]. Notably, we have controlled for these potential confounders as well as for maternal age, mode of delivery, follow-up time, and birth weight yet the association of preterm and of early-term delivery to later pediatric urinary infectious morbidity of the offspring remains significant. Similarly, as the study period spans for over 20 years, we opted to assess the influence of the period in which the child was born on the association between gestational age and later childhood urinary infectious morbidity. We constructed a separate regression model which was specifically controlled for the child's year of birth and the model remained significant. This proves that the association between gestational age at birth and later urinary infectious morbidity is independent of the child's year of birth. Lastly, it is important to separate induced from spontaneous preterm or term birth when evaluating the impact of gestational age on offspring outcome. Since the cohort was not large enough to evaluate spontaneous deliveries only, we constructed a separate regression model controlled for induction of labor. The model remained significant, proving that the association between gestational age at birth and later urinary infectious morbidity was independent of the presence or absence of labor induction.

The main limitation of this study relates to its retrospective nature. As such, only association, rather than causation is presented. A second limitation is that the study included only hospitalizations related to infectious urinary morbidity. No information on urinary infectious morbidity cared for in an ambulatory setting was available for analysis. Thus, generally low rates of cystitis and other urinary infections were found, as only the severe end of the spectrum was included. On the other hand, we present a very large non-selective population-based cohort, with a long follow-up time. A third limitation is that preterm born offspring are always more likely to be admitted to the hospital due to existing co-morbidities. We do not have information regarding the initial cause for hospitalization. Therefore, an existing co-morbidity in these patients may have been the trigger

for these hospitalizations. However, it is unlikely that UTI would be a background disease and not the primary reasons for admission.

Our findings suggest that early-term period exhibits similar characteristics to those of the late preterm period in terms of susceptibility to urinary infections, thereby adding another consideration to the optimal delivery timing discussion. Even within term gestation, different gestational ages may carry a different impact on later offspring health. The clinician should be made aware that prematurity probably affects the maturity of the urinary system in addition to the more commonly cited respiratory and neurological systems. This can cause increased susceptibility to urinary infection during childhood. This study thus adds to the accumulating evidence that delivery at early term bears negative consequences on the child's future health in a perhaps broader perspective than previously thought. Further studies are required to substantiate our findings and determine the specific pathophysiological processes involved.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E (2009) Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet 280(1):7–11. https ://doi.org/10.1007/s00404-008-0836-8
2. Moster D, Lie RT, Markestad T (2008) Long-term medical and social consequences of preterm birth. N Engl J Med 359(3):262–273. https://doi.org/10.1056/NEJMoa0706475
3. Spong CY (2013) Defining "term" pregnancy: recommendations from the Defining "Term" Pregnancy Workgroup. JAMA 309(23):2445–2446. https://doi.org/10.1001/jama.2013.6235
4. Sengupta S, Carrion V, Shelton J, Wynn RJ, Ryan RM, Singhal K, Lakshminrusimha S (2013) Adverse neonatal outcomes associated with early-term birth. JAMA Pediatr 167(11):1053–1059. https://doi.org/10.1001/jamapediatrics.2013.2581
5. Dietz PM, Rizzo JH, England LJ, Callaghan WM, Vesco KK, Bruce FC, Bulkley JE, Sharma AJ, Hornbrook MC (2012) Early term delivery and health care utilization in the first year of life. J Pediatr 161(2):234–239.e231. https://doi.org/10.1016/j.jpeds.2012.02.005
6. Engle WA, Tomashek KM, Wallman C (2007) "Late-preterm" infants: a population at risk. Pediatrics 120(6):1390–1401. https://doi.org/10.1542/peds.2007-2952
7. Paz Levy D, Sheiner E, Wainstock T, Sergienko R, Landau D, Walfisch A (2017) Evidence that children born at early term (37–38 6/7 weeks) are at increased risk for diabetes and obesity-related disorders. Am J Obstet Gynecol 217(5):588.e581. https://doi.org/10.1016/j.ajog.2017.07.015
8. Gutvirtz G, Wainstock T, Sheiner E, Landau D, Walfisch A (2018) Pediatric cardiovascular morbidity of the early term newborn. J Pediatr 194:81–86.e82. https://doi.org/10.1016/j.jpeds.2017.09.060
9. Walfisch A, Beharier O, Wainstock T, Sergienko R, Landau D, Sheiner E (2017) Early-term deliveries as an independent risk factor for long-term respiratory morbidity of the offspring. Pediatr Pulmonol 52(2):198–204. https://doi.org/10.1002/ppul.23529
10. Walfisch A, Wainstock T, Beharier O, Landau D, Sheiner E (2018) Early term deliveries and the risk of pediatric obstructive sleep apnoea in the offspring. Paediatr Perinat Epidemiol 31(2):149–156. https://doi.org/10.1111/ppe.12342
11. Engle WA (2011) Morbidity and mortality in late preterm and early term newborns: a continuum. Clin Perinatol 38(3):493–516. https://doi.org/10.1016/j.clp.2011.06.009
12. Hanna-Wakim RH, Ghanem ST, El Helou MW, Khafaja SA, Shaker RA, Hassan SA, Saad RK, Hedari CP, Khinkarly RW, Hajar FM, Bakhash M, El Karah D, Akel IS, Rajab MA, Khoury M, Dbaibo GS (2015) Epidemiology and characteristics of urinary tract infections in children and adolescents. Front Cell Infect Microbiol. https://doi.org/10.3389/fcimb.2015.00045
13. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A (2010) Risk of renal scarring in children with a first urinary tract infection: a systematic review. Pediatrics 126(6):1084–1091. https://doi.org/10.1542/peds.2010-0685
14. Melville JM, Moss TJ (2013) The immune consequences of preterm birth. Front Neurosci 7:79. https://doi.org/10.3389/fnins.2013.00079
15. Strunk T, Currie A, Richmond P, Simmer K, Burgner D (2011) Innate immunity in human newborn infants: prematurity means more than immaturity. J Matern Fetal Neonatal Med 24(1):25–31. https://doi.org/10.3109/14767058.2010.482605
16. Marodi L (2006) Innate cellular immune responses in newborns. Clin Immunol 118(2–3):137–144. https://doi.org/10.1016/j.clim.2005.10.012
17. Nielubowicz GR, Mobley HL (2010) Host-pathogen interactions in urinary tract infection. Nat Rev Urol 7(8):430–441. https://doi.org/10.1038/nrurol.2010.101
18. Spencer JD, Schwaderer AL, Becknell B, Watson J, Hains DS (2014) The innate immune response during urinary tract infection and pyelonephritis. Pediatr Nephrol 29(7):1139–1149. https://doi.org/10.1007/s00467-013-2513-9
19. Dowling DJ, Levy O (2014) Ontogeny of early life immunity. Trends Immunol 35(7):299–310. https://doi.org/10.1016/j.it.2014.04.007
20. Behzadi E, Behzadi P (2016) The role of toll-like receptors (TLRs) in urinary tract infections (UTIs). Cent Eur J Urol 69(4):404–410. https://doi.org/10.5173/ceju.2016.871
21. Song J, Abraham SN (2008) TLR mediated immune responses in the urinary tract. Curr Opin Microbiol 11(1):66–73. https://doi.org/10.1016/j.mib.2007.12.001

22. Förster-Waldl E, Sadeghi K, Tamandl D, Gerhold B, Hallwirth U, Rohrmeister K, Hayde M, Prusa AR, Herkner K, Boltz-Nitulescu G, Pollak A, Spittler A (2005) Monocyte toll-like receptor 4 expression and LPS-induced cytokine production increase during gestational aging. Pediatr Res 58(1):121. https://doi.org/10.1203/01.PDR.0000163397.53466.0F

23. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE (2012) National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 379(9832):2162–2172. https://doi.org/10.1016/S0140-6736(12)60820-4

24. Shapiro-Mendoza CK, Tomashek KM, Kotelchuck M, Barfield W, Nannini A, Weiss J, Declercq E (2008) Effect of late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatrics 121(2):e223–e232. https://doi.org/10.1542/peds.2006-3629