The voiding pattern in healthy pre- and term infants and toddlers : a literature review

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The voiding pattern in healthy infants and toddlers: a systematic literature review.

ABSTRACT

INTRODUCTION

The past decade the views on gaining bladder control have changed. For a long time voiding was believed to be induced by a constant bladder volume [22,29] which means that infants void automatically without interaction of the brain. Lately, brain interaction is detected in the regulation of bladder function in the neonatal period [29,35]. In healthy newborns bladder volume varies. Remarkably, higher bladder volumes when the filling phase occurs during sleep are observed, suggesting a different regulation. [13] Here voiding is accompanied by cortical arousal.[35,37] This suggest an anatomically, but supposedly immature developed pathway of the voiding reflex to the cerebral cortex.[29,30] If the process of acquiring bladder control is only related to maturation and no detrusor-sfincter coordination is detectable, toilet training will not be of any benefit.[19] However a dyscoordinated voiding pattern can be detected before achieving bladder control.[1,11,16,17,30,35]. Generally, toilet training in Western culture starts between 18 and 24 months.[31] At this age a child is assumed to have procured the competences needed for bladder control. Nevertheless, under the influence of social and cultural factors infants can achieve a degree of bladder control at the age of nine months.[5]

Few data are available on voiding patterns in children before they reach bladder control, mainly due to the invasive nature of cystometry. The use of the four-hour voiding observation [13], creates the ability for researchers to study some voiding parameters. Others can be obtained by calculation.[34] Flow and urodynamic patterns in infants have not been clearly defined. They differ from the ones in older children[28], so recognizing abnormalities is not easy [13].

As the knowledge of references values of parameters concerning micturition serve as a guide to knowledge of the existence of a specific condition [23], the aim of this systematic review is to try to obtain a more comprehensive picture of normal voiding pattern in healthy infants, who have not yet reached bladder control.

METHODS

This systematic literature search was performed according the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20]

Eligibility criteria

To be included in this systematic review, clinical studies (S) had to report results about the voiding pattern (O) in infants or preschool children (P). A study had to the meet following eligibility criteria: 1) healthy human patients between 0- 3 year, 2) parameters related to the voiding pattern as outcome measure, 3) published in English, French, German or Dutch, 4) full text report. Abstracts, letters, editorials, case reports, meta-analyses or systematic reviews were excluded.

Insert table 1 here

Information sources and search strategy

To identify articles related to the voiding pattern of healthy infants, a systematic literature search was performed in Pubmed and Web of Science. The last search was run on October 20, 2014. A combination of keywords, both free-text as controlled terminology (MESH) were used. The construct of the search strategy is presented in table 1. At first, selection criteria were applied on title and abstract. Forty-three studies, which complied with the eligibility criteria, were screened in the second phase on full-text basis. Additionally, reference lists of all included full text studies were hand screened.

Screening was performed independently by two authors (KVdC, AV). In case of disagreement a third author (SDW, GDW) was consulted.

Data items

Data were extracted from each included study on: 1) characteristics of the population, 2) sample size, 3) method of assessment, 4) type of outcome measure and 5) main results.

Insert table 2 here

Risk of individual bias

Methodological quality was assessed with the Scottish Intercollegiate Guidelines Network checklist (SIGN). It was performed by two independent researchers (KVdC, AV) who were blinded to each other. In case of uncertainty a third researcher was consulted (SDW, GDW). The most important

methodological limitations were inadequate information about statistical analyses, confounders and blinding of the patients.

RESULTS

Search Strategy

After consulting the databases, the initial search resulted in 440 papers. Title and abstract were screened for eligibility and 40 studies were deemed relevant. Studies not meeting inclusion criteria were excluded, mainly because the article did not report data about variables related to voiding behavior/ pattern. After the methodological assessment 21 studies were qualified for inclusion. A summary of the applied search strategy can be retrieved in figure 1.

Insert figure 1 about here

Study characteristics

The 21 studies included cohort and cross sectional designs. As presented in table 2 the number of patients varied between 19 [32] and 229 [35]. The age of the patients ranged from a preterm age of 31,3 weeks gestational age [26] to 6 years [16]. The latter study was included because a distinction in the different age groups was made. Fifteen studies were performed in Europe, five in Asia and one in Africa.

Syntheses of the results

Filling phase

Diuresis

Diuresis in preterm infants is larger than in “a term” born children. The hourly urine production (ml/kg/h) of male infants (gestational age 31,3 weeks) is more capacious than the one in “a term” newborns (p<0,01).[26] At the age of 6,5 months, diuresis in preterm infants (5,8 ml/kg/h) (mean age of 32 weeks after cessation of menstrual flow) is 1,8 ml/kg/h higher than in “a term” newborns (4,0 ml/kg/h).[30] It is advocated that diuresis decreases with age.[13] However a great variation is detected in 14 day old “a term” children (range 2,2- 10,1 ml/h/kg).[11]

Bladder capacity

A higher diuresis leads to a higher maximal voided volume (r=0,43, p<0,005)[11], which increases parallel with bladder capacity [36]. The latter is defined as the sum of the voided volume and post void residual urine volume. Different formulas are suggested to calculate bladder capacity.[1,13] No consensus about a possible gender difference is reached.[1,33] Generally it can be stated that the bladder capacity increases with age.[6,13,16,17] A significant change in bladder capacity was first seen at the interval 0,5-1y (p=0,002) and a second time at the interval 2-2,5 years (p=0,043).[16] Additionally it is detected that the lowest mean bladder volume triggering micturition (voided volume + post voiding residual urine) also merges with age.[6,17] Additionally, when comparing Swedish with Vietnamese children, the latter had the lowest bladder capacity and smaller lowest volumes triggering micturition in all age categories.[7] (figure 2)

Insert figure 2 here

The influence of body weight on these parameters is not fully understood. Holmdahl et al. 1996 stated that diuresis decreases with weight according to 8,1- 0,5 x weight (kg) (R^2=36%, p=0,001)[13], while Gladh et al. (2000) reported no correlation (r=0,07, p=0,65).[11] No significant correlation between bladder capacity and body weight was scrutinized.[7,13]

Emptying phase

arousal

Bladder voiding may ensue with or without awakening [39], however most voids in infants occur when being awake [11,17], or the infants awake immediately before voiding [13,36]. Sixty percent of the “a term” born infants voided when being awake. This percentage is as much as the double of the awake voiding percentage in preterm infants (30%).[4] During micturition overt signs of arousal and body movements were consistently detectable.[36] But even when infants do not awake actively during voiding a significant change in sleep pattern can be detected. A shift from quiet sleep to an active REM or indeterminate sleep - associated with limb or facial movements - can be distinguished. When no body movement is present, a change in heart rate and respiratory rate, companioned with a change in sleep pattern during micturition, was detected.[36,39] Overall, this suggest that during sleep

voiding cortical arousal can be present.[39] The term arousal encompasses a change in EEG accompanied with at least 2 of following criteria: 1) body movements, 2) change in heart rate, 3) change in breathing pattern (frequency or amplitude during quiet sleep), 4) an increase in EMG amplitude during active sleep.[37] It arose in 33 %- 57% [30,32,40] of all preterm micturitions, while in more than 90% of the healthy “a term” newborn males arousal was detected [24,37]. Concerning heart rate and EEG frequency, preterm infants showed no significant difference. However, a raise in the 5 second interval before and after voiding compared to the 30 second period before voiding was detected in “a term” infants.[37] Nonetheless it should be noticed that in preterm infants no significant correlation between body movements at the beginning of micturition and gestational age, nor with postnatal age or actual body weight was encountered. [40] (figure 3)

Insert figure 3 here

Flow curve

In healthy newborn males, the level of arousal did not differ with diverse flow curve shapes (p= 0,45).[24] A dyscoordinated flow is assessed during free voiding with an ultrasound probe. Olsen et al. labelled this as the collection of: flows which show fluctuations of more than 1/4 of Q max (staccato), fluctuated flows and interrupted flows. Ninety-five percent of the premature male infants (median gestational age 31,3 weeks) with a voiding frequency >1/4h, had at least one coordinated flow curve.[26] In “a term” newborns, 35 % of the voids are constantly coordinated.[24,26] The notable unexpected finding is that although a coordinated flow pattern was discerned in 66% of “a term” neonatal flow curves, a decrease in coordinated voids was detected with ageing. Only 54% of the infants, aged 9,2-19,8 months voided coordinated, assuming that bell and tower shaped curves constitute coordinated voids.[25] Despite the large percentage of coordinated voiding, other flow curves such as staccato, tower, plateau and spike dome are also seen.[24-26] Amongst a 4-hour voiding observation only notice of interrupted voiding can be made. A generally accepted definition of interrupted voiding is: “two or three voids within a period of 10 minutes leaving the lowest post-void residual volume after the last micturition”.[6,17,30] In general, interrupted voiding decreases with age.[6,7,17] In preterm infants (gestational age 32 weeks) this is present in 58-70% of all voids, whereas in “a term” children this ranges from 23 to 40%.[4,30] The phenomenon is rarely detected in infants older than 1 year, when toilet training was introduced.[6,13] However, compared to Vietnamese

children, interrupted voiding remained longer present in Swedish children.[7] No gender difference could be distinguished.[30] (figure 4)

Insert figure 4 here

Flow rate

In general the average ultrasound maximum flow rate increases with age according to 4,1 ± 1 ml/s (< 1 year) or 8 ± 3 ml/s (1-3 year).[34] Premature children have a lower flow rate than “a term” born children.[26]

Voiding pressure

Maximum voiding pressure in males (0,3-3,9 months: 127 cm H2O (range 84-211 cm H2O) is higher than in female infants (0,2-7,3 months: 72 cm H20 (range 42-240 cm H2O) (p<0,01).[1] Interestingly is the fact that in crying males the voiding pressure raises (crying median maximum 151 cm H2O versus non-crying median max 113 cm H2O documented with electromyography) while contrasting, in females pressure lowers (crying median maximum 78 cm H2O versus median maximum non-crying 101 cm H2O documented with electromyography).[1]

Voided volume

Voided volume is nog significantly related to the flow curve pattern (p=0,09).[25] Nonetheless, it tended to be larger in plateau shaped flow curves (p=0,05).[24,26] Voided volume increases significantly according to age [7,13], especially after the first six months of life.[36] The voided volume of preterm infants is generally smaller than of “a term” born infants (p< 0,05).[4,30] It ranged in preterm infants from 6,7- 14,1 ml [32,33], whereas in “a term” infants the voided volume can be as large as 77 ml [11]. In the latter population a significantly increase is detected at day 1- 4 (p< 0,05) and at day 14-28 (p< 0,01)[4]. This differs from the preterm born children where the interval is situated only at one time period: day 14-28.[4] (figure 5)

Insert figure 5 here

Expressed as a percentage of the estimated bladder capacity (EBC), the mean voided volume did not change with age (range 37% - 100%).[13] Fourty-two percent of the 9 to 20 months old infants have at least one void of more than 65% of EBC (age (years) X30) + 30).[25] Remarkably the voiding volume

during sleep corresponds with the individual bladder capacity (voided volume + post voiding residual urine volume) in > 50% of infants aged 3 months, but in none at 6 months.[17]

Post void residual urine

PVR in preterm infants (mean gestational age 29 weeks) was 11,9% of EBC, whereas in “a term” children this percentage is smaller (8,8%).[30] However a range in PVR of 0 – 22% was encountered (aterm, 1,8-12,3 months).[13] Considerably, a variation of 7-25% is described of all voids occurring without PVR.[13,33] In 42% of 3-7 day old infants (mean gestational age 34 weeks) no PVR was addressed after at least one void per 4 hours.[30] Jansson et al.(2000) even noticed that 85% - 100% of infants aged 0-3 years have a PVR lower than 5 ml (measured with US) at least once per 4 hours (mean 7 ml).[17] Fourty-one percent of 1,8-12,3 months old children had a PVR < 5ml (mean 4,6 ± 3 ml, range 0-13 ml).[13] The same trend could be detected in preterm infants where PVR diminishes from a mean PVR 1,7 ml (range 0-7 ml, 95% CI 0,9-2,4) [30] to 1,2 ml [32]. Conclusively, PVR decreases slowly over time and shows large variations in age groups.[6,17] (figure 2) In contrast, Holmdahl et al. 1996 stated that PVR did not change with age.[13] Noticably, the mean PVR of male (1,9 ml) preterm infants is greater than of females (0,9 ml), while in “a term” newborns no gender difference was detected.[33] [7]

No correlation of voided volume with body weight of an infant could be detected.[7]

Voiding frequency

During the first few days of life, voiding frequency (VF) is very infrequent.[36] No significant change was detected in VF between exclusively or partially breastfed neonates.[8] VF was in 59% of the exclusive breastfed > 8x/day, but also in partially breastfed infants this percentage remained 55,8%.[8] Premature children have a higher VF than “a term” infants [26] (at 1 year: mean 3,3x/4h [13]↔ 3,8x/4h [17]). In preterm infants (0-28 days, mean gestational age 32,7 weeks) a peak is seen at day 1- 4 and from day 4 until day 7 ($p < 0,01$), followed by a significant decrease at the age of 2 weeks to 28 days ($p < 0,05$).[4] Whereas, in “a term” infants VF only increased significantly at day 4-7.[4] This contrasts with the statement that VF increases rapidly after the first week and peaks at the age of 2 weeks (4x/4hours)[17]. VF decreases with age, especially during the first year of life.[13,36] According to Jansson et al. VF declines from a mean value of 4,7 (0 years) to 3,8 (1 year), over 3,4 (2 years) to

2,2 in 3 year old infants.[17]. No differences were found in voiding frequency between male and female infants.[36] Vietnamese infants had a lower VF (mean 3,5/4h at 3 months age → 3X/4h at 24 months) than Swedish children.[7]

Eregie et al.1998 argues that birth weight has an influence on voiding frequency.[8] A VF of more than 8x/day was notable in 60% of infants with a birth weight ≥ 2,500 kg compared to 27,3% of low birth weight children (<2,500 kg). Remarkable, 48,5% of the exclusive breastfed low birth weight infants had a VF < 5x/day, whereas in infants ≥ 2,500 kg this is 16%.[8]

DISCUSSION

The review set out with the aim of addressing the normal voiding pattern described in scientific literature. Psychometrics that were investigated in literature were signs of arousal, voiding volume and bladder capacity, flow rate, voiding frequency, diuresis, post voiding residual volume, voiding pressure, interrupted voiding and detrusor stability and flow curve.

The most interesting finding was that there is a great inter- and intra-individual variability among all voiding parameters. Little evidence was found concerning the correlation between signs of arousal during micturition and gestational age [40], actual body weight [40], flow curve [24] or postnatal age [40]. Although voiding in infants older than 12 months was mostly accompanied with over signs of arousal [36] and body movements, no consensus was reached on the relationship with postnatal age.[40] This inconsistency may be due to the fact that process of voiding is not yet been completely clarified.[38] It has been assumed that there is a relationship between the onset of REM sleep (eye movement period) and micturition during 37-41 weeks of gestation, but not at 33-36 weeks.[10] This suggest a neuronal development of descending control of fetal micturition whereby the closely relationship between the locus coeruleus and peri alpha (REM sleep) and the control center of micturition (the dorsolateral tegementum, pons) becomes obvious in the human “a term” fetus.[18] The finding that bladder voiding in infants is accompanied with a change in heart rate, which is associated with internal stimuli, stipulates the hypotheses that a change in heart rate is affiliated with cortical arousal.[38] Probably, “a term” infants possess a functional spino-pontospinal voiding pathway by which, combined with cortical arousal mechanisms, the lowest volume triggering micturition is influenced.[11,21] This refutes the earlier assumption that the process of micturition initiates automatically without cortical influence.[12] However, there is such great inter-and intra-variability in

bladder volume triggering micturition, that the plausibility of this assumption decreases. The variation of the volume at which voiding is initiated, expressed as a percentage of EBC (0-3 years: 3-100%)[17], might indicate that infants can postpone consciously voiding. [9]

It is also interesting to note that flow rate increases with age.[34] Although VF multiplies rapidly in the first weeks of life it diminishes with age [13,36]. This great variability might be related to the amount of feeding during assessment. Fluid intake will be higher when breast milk feeds occur with a nasogastric tube (volumes vary from 150ml/kg/24h [26] at intervals of 3 hours to 28ml/kg/4h [32]). However, infants who had established breastfeeding, only have fluid intake when feeling hungry. This difference in time of feeding must be kept in mind when interpreting voiding frequency and diuresis. Breast feeding during the first days of life has a significant influence on the voiding frequency.[3] This conclusion differs from that of Eregie et al.1998 who detected no significant change in VF between exclusively or partially breastfed neonates.[8] It is suggested that gestational maturity, which relates with birth weight has an influence on the voiding frequency due to the effect on renal functional maturation and the possible different threshold for the intravesical pressure required for initiating the micturition reflex (presuming that voiding initiates automatically).[8] However, no consensus is reached. The statement that birth weight is related to diuresis is supported by Gladh et al. (2000), in contrast Holmdal et al. (1996) highlights a diminution of diuresis. Restricting fluid intake might have implications on VF and diuresis since a positive correlation was detected between voiding frequency and diuresis.[11]

PVR subsides with age and shows large age related variations.[17] Previous research has demonstrated that infants do not completely empty the bladder at every void.[13,24,27] Both preterm as “a term” newborns have a small amount of residual urine.[30] A first clarification herefore is the incapacity to sustain the detrusor contraction.[30] A second possible explanation is the fact that a dyscoordinated flow pattern was discerned in just 34% of the neonatal flow curves. In none of premature male voids a coordinated flow was detected [26], whereas 35 % of the “a term” newborns had one [24,26]. An immature coordination between urethral sphincter and detrusor, leading to a premature interruption of the urinary stream, might cause interrupted voiding [14], a factor declining with age.[6,7,17] It might be hypothesed that interrupted voiding is related to detrusor muscle instability. However this does not seem likely since even infants have a relative stable bladder.[17] Since males have higher voiding pressures than females [1,15], it can be argued that normalization of this high voiding pressures will occur with an improvement of detrusor-sphincter dyscoordination.

Nonetheless, lower levels of voiding pressure in female infants are detected, in spite of the fact that they also have dyscoordinated patterns. The study of Ichino et al. (2007) stated that the dyscoordinated contractile response of the detrusor to the sphincter decreases with age. This suggest that the high pressure levels in males are due to the fact that there is a detrusor- sphincter dyscoordination combined with a possible detrusor hypercontractility. The divergence between male and female infants might be caused by the difference in anatomically length of the urethra.[15,29] However this remains controversial.

Ninety-five percent of the premature and newborn male infants had at least one bell-shaped flow curve.[24,26] Other seen flow curves are staccato, tower, plateau and spike dome.[24-26] The spikes in the latter might be explained by an early relaxation of the pelvic floor or urethral sphincter just before the detrusor contraction.[24] Normally, divergent curves can be indicative for obstruction. However, since such a high percentage of infants presented a bell-shaped curve, this is highly unlikely.

Relevant studies might be missed by focusing only on two databases and controlled terminology. By including only original studies, written in English, interesting studies can be eliminated. All studies have relatively small sample sizes. A possible explanation is that since the measurement of voiding parameters in healthy infants by urodynamics is not ethically accepted, most studies obtain data by the four hour observation method.

Given some inconclusive findings and the low levels of evidence due to the observational designs, further research is warranted. In many studies factors known to be related with micturition are not investigated. Hereby it is possible that influencing factors are missed and correlations are not detected.

The recognition of all parameters related to voiding and possible effecting it, is important to fully understand the mechanism of micturition. In Western culture it is seen that the age of acquiring bladder control is altered[2]: only 5% of Swedish children had started potty training on 24 months, while in Vietnamese cultures 88% of the infants aged six months are on daily potty training.[6] This may have on long term, socio-economic consequences because of increased use of diapers and refusal of starting in nursery class. Up to now it remains unclear whether voiding is an automatically process or is influenced by cortical mechanisms. Evidence for the latter remains inconclusive.

Conflicts of interest: The authors declare that they have no conflict of interest

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