Positioning and complications of umbilical catheters

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CHAPTER 8

Thrombosis after umbilical venous catheterization: prospective study with serial ultrasound

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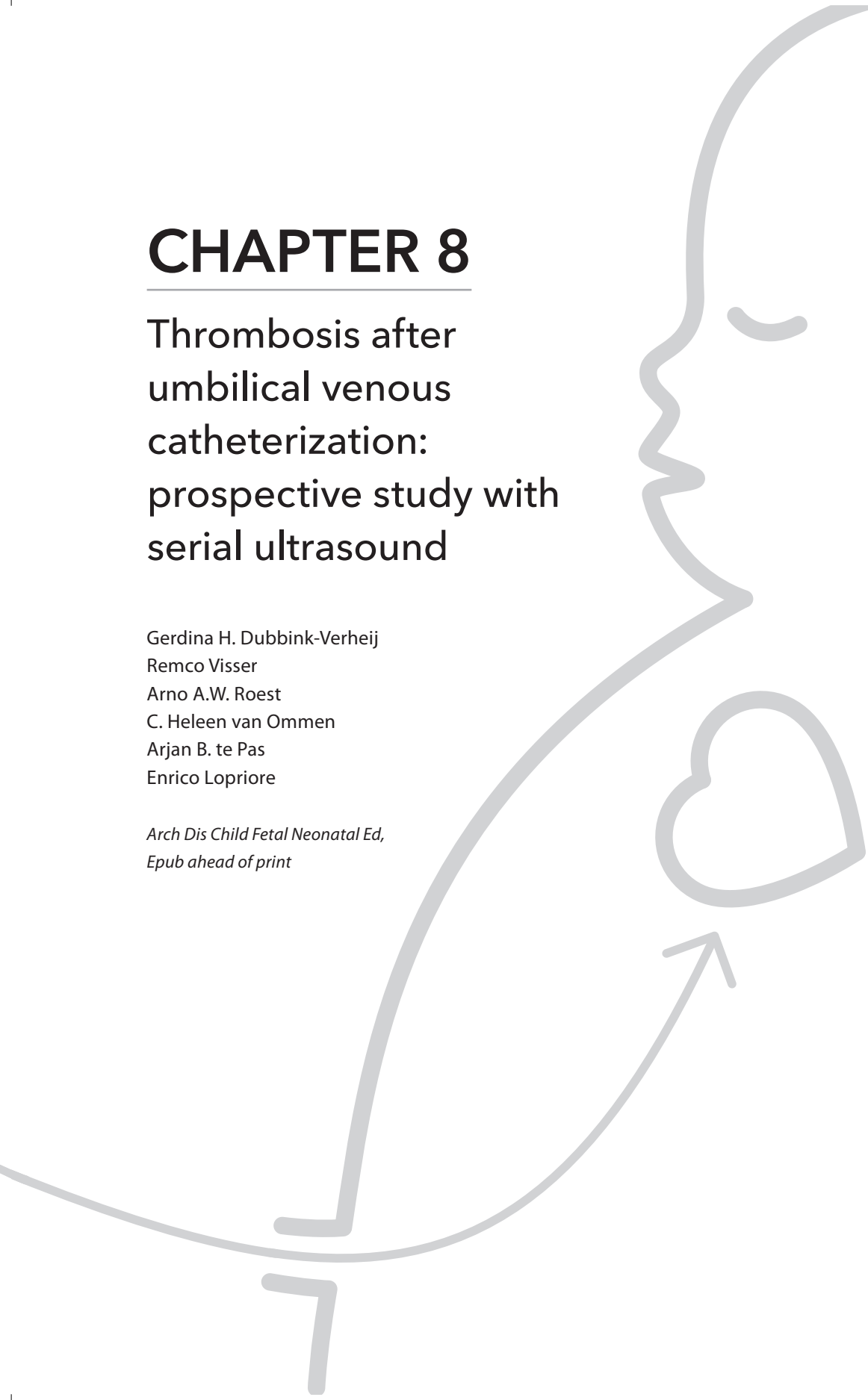

ABSTRACT

Background

Umbilical venous catheters (UVCs) are associated with thrombus formation. Most studies on thrombosis in infants with UVCs focus on only one part of the route, and none assessed a control-group of infants without UVCs.

Objective

To determine the incidence and location of thrombi in infants after umbilical catheterization, and compare this with a control-group of infants without umbilical catheters.

Design

Prospective observational study with serial ultrasonography of the UVC route from the umbilico-portal confluence to the heart. Ultrasonography was performed until day 14 after catheterization in cases and day 14 after birth in controls.

Results

Thrombi in the UVC route were detected in 75% (30/40) of infants with UVCs in the study-group, whereas no thrombi were detected in the control-group of infants without UVCs (0/20) ($p<0.001$). Six thrombi (20%) were located in the right atrium. Most of these were also partly present in the ductus venosus. Six thrombi (20%) were located in the ductus venosus only, and in 12 infants (40%) the thrombus was at least partly located in the umbilico-portal confluence. Thrombi persisted after UVC removal in 25/30 cases. Two infants with thrombotic events were treated with low-molecular-weight heparin and resolution was found. In the other 23 infants managed expectantly, 2 died due to necrotizing enterocolitis, 1 was lost to follow-up and in 20 spontaneous regression was seen.

Conclusions

Thrombotic events occur frequently in infants after umbilical catheterization. Most thrombi were asymptomatic and regressed spontaneously with expectant management. Routine screening for thrombi in UVCs is therefore not advised.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Umbilical venous catheters are associated with thrombus formation.
- The incidence of thrombosis in infants without umbilical venous catheters is unclear.

WHAT THIS STUDY ADDS

- Most infants have thrombosis in the umbilical venous catheter route after umbilical venous catheterization.
- Thrombosis in the umbilical venous catheter route in infants without umbilical venous catheters is not detected.
- Routine screening for thrombi in umbilical venous catheters does not seem necessary as most are asymptomatic and regress spontaneously.

INTRODUCTION

Umbilical catheters are frequently required for the management of critically ill infants. Umbilical venous catheters (UVCs) are used for intravenous administration of parenteral nutrition and medication. These catheters are relatively easy to insert, and may be used for a longer period as compared to peripheral iv access. However, the advantages of UVCs should be balanced against the potential risks. Central venous catheterization is reported to be the most common cause of neonatal thrombosis.[1, 2] Catheter-associated thrombosis may be asymptomatic but may also result in thrombocytopenia, infection, pulmonary embolus, liver necrosis and, occasionally, even death.[3-5] Reported incidence of UVC-related thrombosis varies greatly from 2.2% to 43% due to differences in study design and methodology.[6-13] UVCs are introduced in the umbilical vein to reach the umbilico-portal confluence, and subsequently pass the ductus venosus to reach the junction between the inferior vena cava (IVC) and right atrium, which is the ideal location for the UVC tip.[5, 14] The tip of UVCs is positioned too high when it is located in the right atrium or passing through the patent foramen ovale, within the left atrium or pulmonary vein.[15] Too low positioned UVCs have their tip in or below the umbilico-portal confluence or are malpositioned, for example in the portal vein. Thrombus formation may occur in all parts of this UVC route. Most studies on thrombosis in infants with UVCs focus on only one part of the route, such as the liver or heart, not determining the incidence of thrombus formation in all locations together.[6-11] None of these studies investigated the occurrence of thrombosis in the UVC route in infants without UVCs.

The aim of this study was to determine the incidence and location of thrombi in infants after umbilical catheterization with ultrasonography in the entire UVC route and to investigate if thrombosis in this route exists in infants without umbilical catheters.

METHODS

We conducted a prospective observational study at the neonatal intensive care unit of the Leiden University Medical Center, a tertiary care center in The Netherlands. The study was approved by the hospital system institutional review board. Written informed consent was obtained from the parents of participating infants.

Infants of all gestational ages were considered for enrollment in the study-group if a UVC was inserted. Infants were included from October 1st 2016 until October 1st 2017. We aimed for a convenience sample of 40 infants with and without UVCs during this period.

Umbilical catheterization was performed according to local protocol. Estimated insertion length of the UVC was calculated based on the revised formula of Shukla.[16] An antero-posterior chest X-ray was routinely performed in all cases to determine

the position of the catheter. Within an hour after catheterization, the position of the catheter-tip was determined by ultrasonography as well, and the presence and location of a thrombus was noted. Ultrasonography was performed by skilled neonatologists or pediatric cardiologists. Correct position of the UVC was defined as a UVC with the catheter-tip in the ductus venosus or at the junction of the ductus venosus and IVC/right atrium by ultrasonography (see Figure 1). Only infants with UVCs in the correct route with the catheter-tip having passed the umbilico-portal confluence could be included in the study. Infants with UVCs positioned too low or with the catheter-tip in blood vessels in the liver were excluded, because these UVCs were removed within one hour after insertion. These patients were also not eligible for the control-group. UVCs that were positioned too high were pulled back to the correct position after ultrasonography. Ultrasound scans were repeated on day 3, 7 and 14 after catheterization. Additional ultrasound scans were performed on the day of catheter removal. During the study period of one year infants without an indication for a UVC were considered for enrolment in the control-group. Matching cases and controls according to gestational age and birth weight was not possible as all infants below 28 weeks routinely receive umbilical catheters in our department. In the control-group ultrasonography was scheduled within 24 hours after birth, on day 7 and on day 14. In both groups in case of discharge of the patient before day 14 an ultrasound scan was performed within 24 hours preceding discharge. In case of non-availability of a skilled professional to perform ultrasonography, the examination was performed one or two days before or after the scheduled day.

Ultrasonography was performed with a Toshiba Aplio 400 or Aplio i700 machine (Toshiba Medical Systems Europe B.V., the Netherlands) with multi-frequency transducers. Standard two-dimensional gray scale images were acquired from at least subcostal, abdominal and apical four-chamber views, sometimes extended with parasternal short-axis views and were stored in digital format. The heart, IVC, ductus venosus and umbilico-portal confluence were visualized and screened for the presence of thrombi. A thrombus was defined as an echo dense structure within the heart or vessels or around the catheter observed in two dimensions. Except for thrombi in the ductus venosus, thrombi were classified as obstructive or non-obstructive based on the presence or absence of flow around the thrombus. Thrombi in the right atrium were classified as filling more or less than 50% of the atrium. Flow in the ductus venosus ceases within the first minutes to days independent of the presence or absence of a UVC.[17] Thus, flow was not used as a discriminating factor to assess thrombi in the ductus venosus.

Decisions to remove the UVC were made by the attending physician. Decisions to treat thrombi were based on the Dutch national guideline concerning catheter-related thrombosis in neonates.[18] This guideline advises a 'watch and wait' approach in most cases. If thrombi cause complete obstruction of blood flow or rapidly progress without treatment, treatment with low-molecular-weight heparin (LMWH) is advised, as well as

in thrombi filling >50% of the right atrium. Thrombolysis is only advised in cases with high risk of organ- or life-threatening consequences.[18] Follow-up of thrombi after day 14 was performed if considered clinically indicated according to the attending physician.

All above data were recorded. Baseline characteristics of each infant, and clinical data, including gestational age, birth weight, duration of hospital admission, mortality, date and time of UVC placement and removal, timing of ultrasound scans, peripherally inserted central catheter (PICC) insertion after UVC placement, position of catheter-tip and presence and location of thrombosis, were extracted from the electronic patient dossier Metavision (iMD-soft, Leiden, The Netherlands). Presence and timing of necrotizing enterocolitis stage 2a or higher,[19] culture-proven sepsis and thrombocytopenia (defined as a platelet count $\leq 150^{*}10^{9}$/L) and treatment of thrombi were also recorded.

Statistical analysis

Data are given as median with range unless otherwise mentioned. Incidences of thrombosis were compared with the Chi-square test. The student's t-test for parametric and the Mann-Whitney U test for non-parametric data were used for comparisons of continuous variables. P-values below 0.05 were considered significant. All statistical analyses were performed with IBM SPSS Statistics version 23.0 (IBM Software, Armonk, NY, United States).

RESULTS

Patient characteristics

We included 40 infants in the study-group of infants with UVCs and 20 infants in the control-group without UVCs. Patient characteristics in both groups are given in Table 1.

Table 1 – Patient characteristics of infants with UVC (study-group) and infants without UVC (control-group)

Variable	Study-group (n=40)	Control-group (n=20)	p-value
Gestational age at birth (weeks)	27 (24-41)	29 (27-41)	0.06
Birth weight (grams)	1052.5 (600-3925)	1464.5 (1020-3300)	0.07
SGA, n (%)	6 (15)	0 (0)	0.07
Duration of hospital admission (days)	18.5 (3-102)	13 (3-44)	**0.04**
PICC received after UVC, n (%)	12 (30)	3 (15)	0.21
NEC, n (%)	5 (12.5)	1 (5)	0.36
Culture-proven sepsis, n (%)	11 (27.5)	2 (10)	0.12
Mortality, n (%)	4 (10)	1 (5)	0.51

Data are represented as median (range) unless otherwise specified. P-values <0.05 were considered significant. Significant p-values are depicted in **bold**. UVC: umbilical venous catheter. SGA: small-for-gestational-age, defined as a birth weight adjusted for gestational age below the 10th centile according to growth curves for Dutch neonates.[29] PICC: peripherally inserted central catheter. NEC: necrotizing enterocolitis stage 2a or higher.[19]

Four patients in the study-group died, due to necrotizing enterocolitis (n=2) and pulmonary bleeding (n=2), and one patient died in the control-group due to necrotizing enterocolitis (n=1).

Incidence of thrombosis

Thrombi in the UVC route were detected in 75% (30/40) of cases in the study-group, whereas no thrombi were detected in the control-group (0/20) ($p<0.001$). Thrombi were first detected by ultrasonography in 14/30 cases (47%) at day 3-5, 12/30 (40%) at day 6-8, and 4/30 (13%) between day 9 and 15 (median day 6). Thrombi were detected in 9/30 cases after UVC removal, in 4/30 cases at the day of UVC removal and in 17/30 cases before UVC removal. In none of the cases thrombosis was the reason for UVC removal. Thrombi were detected in different parts of the UVC route (Figure 1).

Six thrombi (20%) were located in the right atrium. Five of these thrombi were also partly present in the ductus venosus and one was located along the entire route including ductus venosus and umbilico-portal confluence as well. All right atrial thrombi filled less than half of the atrium and the two thrombi located at the junction of ductus venosus and IVC/right atrium were non-obstructive as well. Six thrombi (20%) were located in the ductus venosus only and in 12 infants (40%) thrombi were at least partly located in the umbilico-portal confluence.

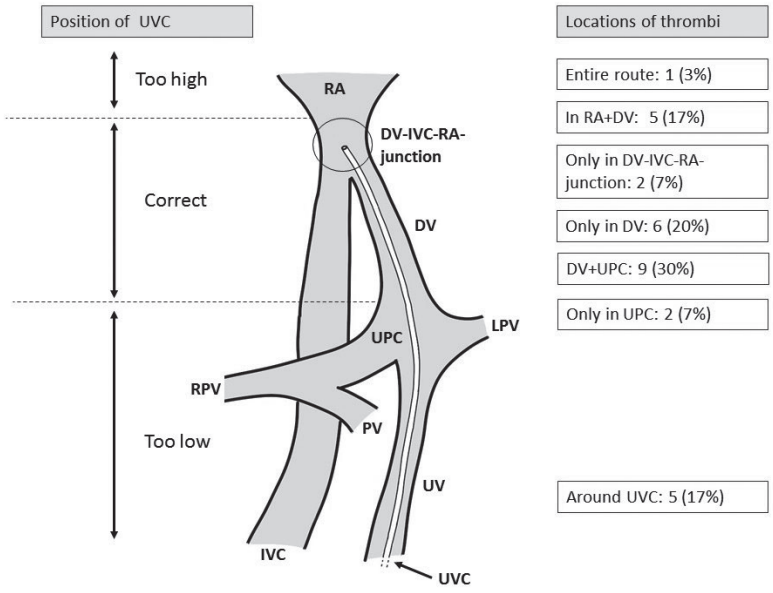

Figure 1. Locations of the 30 detected thrombi, n (%). RA: right atrium, DV: ductus venosus; UPC: umbilico-portal confluence, LPV: left portal vein, RPV: right portal vein, PV: portal vein, IVC: inferior vena cava, UV: umbilical vein, UVC: umbilical venous catheter.

Other aspects

Ultrasound data for study-group and control-group are given in Table 2.

Table 2. Ultrasound data in study-group and control-group.

	Study-group (n=40)	Control-group (n=20)
Follow-up duration after UVC insertion (days, median, range)	14 (2-16)	-
Follow-up duration after birth (days, median, range)	-	13 (1-17)
Position of UVC at initial ultrasound		
Correct	5 (13)	-
Too high	33 (83)	-
Not to determine	1 (3)	-

UVC: umbilical venous catheter.

At initial ultrasound 5/40 UVCs (13%) were in correct position, 2/40 (5%) were placed with tips in the left atrium, and 31/40 (78%) in the right atrium. In one UVC the exact position of the tip could not be determined due to limited visualization of the catheter by ultrasonography and in one ultrasonography was not performed directly after catheterization. Thrombus data of these cases are included in the analysis. Thrombocytopenia was seen in 6/40 infants with UVCs (15%) and in 2/20 controls (10%) (p=0.59) during admission. One infant with thrombocytopenia in the UVC-group had no thrombus in the UVC route. In 3 infants with thrombocytopenia, this was observed before and in 2 after detection of the thrombus. In 4 cases, thrombocytopenia was interpreted by the attending physician as a possible symptom of thrombosis. Two infants with thrombi had persistent catheter-related sepsis with *Staphylococcus aureus*. No other symptoms of thrombosis, such as loss of UVC patency were noted.

Follow-up of infants with catheter-related thrombi

Four of the 30 detected thrombi were visualized around the catheter and could not be visualized anymore after removal of the catheter. One infant with a thrombus around the UVC was lost to follow-up. The other 25 thrombi persisted after removal of the catheter. Two of 25 patients were treated with LMWH with resolution of the thrombus as a result. One, with thrombus formation in ductus venosus and umbilico-portal confluence, was treated because a thrombus in both venae iliacae communes developed after placement of another central venous catheter (CVC) and the other because progression of a thrombus in right atrium and ductus venosus during expectative management. All other patients were managed expectantly.

Two of the 25 patients with thrombi died during the neonatal period due to necrotizing enterocolitis. In 12/25 patients follow-up was considered not necessary, as the thrombi regressed spontaneously during the study period or were located in the ductus venosus (a non-functional structure after birth). The remaining 9/25 patients were discharged

home without treatment with persisting thrombi in right atrium and/or umbilico-portal confluence. Thrombi in these 9 cases were non-obstructive, filled less than 50% of the right atrium and were stable during hospital admission. One of these 9 cases was lost to follow-up. At ultrasound follow-up in the outpatient department within one year after term age, the other 8 thrombi all regressed and disappeared spontaneously.

DISCUSSION

In this study, thrombosis in the UVC route was detected with screening by ultrasonography in 75% of infants after umbilical catheterization, whereas no thrombi were demonstrated in the investigated location in infants without UVCs. This result emphasizes that CVCs play an important role in the aetiology of neonatal thrombosis.[20] Studies described that thrombus formation in the UVC route could lead to thrombocytopenia, persistent sepsis, liver damage, portal hypertension, symptoms of right heart failure and pulmonary embolism.[21-23]

We prospectively screened the complete route of the UVC from the umbilico-portal confluence up to and including the heart, whereas previous studies mainly focused on one or two parts of this route. This might explain the higher incidence of UVC-related thrombosis (75%) when compared to previous reports (2.2-43%).[6-13] The incidence of thrombi located only in the umbilico-portal confluence in this study was 30% (12/40), which is comparable to the incidence reported in previous studies. However, the incidence of thrombi located in the right atrium, IVC and ductus venosus was much higher, 58% (23/40) when compared to previous reports (10-30%).[6, 8] The use of novel ultrasound machines with higher sensitivity to detect thrombi compared with the equipment used in the past, may possibly explain the higher incidence of thrombi compared with older studies. Methodological differences related to the use of different ultrasound screening programs or differences in the screened population may be an explanation as well. Suggested risk factors for catheter-related thrombosis, such as being small-for-gestational-age, dwelling time of the UVC, and the use of parenteral nutrition could differ in our population compared to others and be of influence on the incidence of thrombosis.[22] However, the sample size of our group is too small to confirm the influence of risk factors.

Neonatal thrombosis is in 89-94% of cases catheter related, but reliable data on thrombosis in infants without catheters, especially in the UVC route, are not available.[2, 20] The ductus venosus is a fetal structure that after birth closes permanent with fibrotic transformation into the ligamentum venosum. Some authors suggest thrombus formation contributes to this process as well.[17, 24] However, we did not observe this in our study. Hence, although our control-group was just a small group of infants, the thrombotic incidence of 0% in this group is an important finding.

Neonates are at increased risk of thrombosis due to small vessel diameters and disruption of haemostatic balance by numerous acquired and prothrombotic disorders.[5, 21, 22, 25] Intravascular catheters can cause thrombosis by damaging the epithelium and introducing a foreign thrombogenic surface.[5] In clinically unstable infants at increased risk of thrombosis, CVCs are needed to provide optimal neonatal care. The umbilical vein was for decades an obvious possibility for catheterization and, in many cases, the first choice to get intravenous access in infants. The high incidence of thrombosis in infants with UVCs demonstrated in this study suggest that our policy on use of UVCs needs to be reconsidered. However, CVCs are frequently needed in sick infants and other types of central catheters than UVCs are associated with thrombosis as well. Replacement of the UVC by another type of catheter may not necessarily lead to less complications.[6, 13, 22, 26, 27]

Management of UVC-related thrombi is based on expert opinion guidelines and the impact of these thrombi on outcome is not clear.[20-22, 26, 28] As shown in our study, spontaneous resolution of UVC-related thrombi detected by screening is likely to occur. Therefore, a 'watch and wait' approach in asymptomatic thrombi detected by screening with ultrasonography may be justified.[26] However, it is unclear how many infants with catheter-related thrombi will develop long-term consequences later in childhood. To determine the natural history, and possible consequences of catheter-related thrombosis a larger prospective study is needed. Currently, a prospective study in neonates with thrombi is being performed in the Netherlands (the Neoclot study).[18] Because clinical implications of thrombi are not clear yet, and most thrombi detected by screening disappear spontaneously, routine screening apart from research settings cannot be advised. This is also confirmed by Haddad et al, who report that the majority of catheter-related thrombi they detected was stable and detection led infrequently to changes in patient management.[28]

Care should be taken when interpreting the results of our study due to several limitations, including the relatively small number of patients. In addition, we excluded infants with UVCs positioned too low or malpositioned with catheter-tips in veins in the liver, because these catheters were removed shortly after catheterization and not used. It would have been interesting to know the incidence of thrombi in this separate group, with catheters being in situ for a very short period.

In conclusion, our study demonstrates that thrombi are frequently detected after umbilical catheterization by ultrasonography. Most thrombi are asymptomatic and disappear without treatment. Thus, routine screening for thrombi in UVCs is not advised. However, given the high risk of thrombus formation in UVCs, these catheters should be used with caution and removed promptly if the clinical indication is no longer present.

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