Positioning and complications of umbilical catheters

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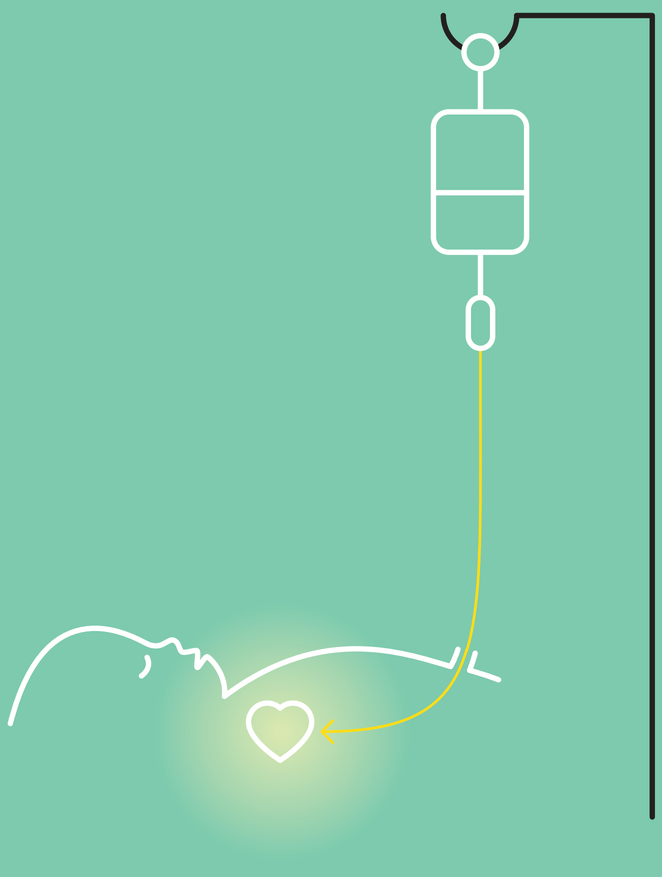

PART III

Review, General Discussion and Summaries

CHAPTER 11

General discussion and future perspectives

Umbilical catheterization (UC) is a procedure frequently performed on neonates with cardiorespiratory instability.[1] While performing the procedure, caregivers often neglect to take the possibility of complications into account, although many different - even potentially devastating - complications are described in the literature.[2-5] In particular the risk increases when the catheter is positioned incorrectly,[5-7] and for this reason avoiding malposition is essential.

The aim of the research described in this thesis was to optimize the positioning of umbilical catheters and thus decrease the risk of complications. Many methods are currently used to ensure that umbilical catheters are positioned correctly, but considerable uncertainty still exists about their accuracy and feasibility. There are a large number of complications associated with the use of umbilical catheters, both frequent and rare. We chose to focus on cardiac arrhythmia, bloodstream infection, and thrombosis in relation to umbilical venous catheters (UVCs), and on hypothermia in relation to the procedure of UC.

In the conclusion of this chapter we weigh up the risks and benefits of the use of UVCs and discuss future research perspectives.

A) METHODS TO PREDICT CORRECT INSERTION LENGTH OF UMBILICAL CATHETERS

The ideal anatomical location for the tip of a UVC is the junction of the inferior vena cava and right atrium (IVC-RA junction),[8-13] and the ductus venosus is also generally considered to be correct.[6, 11] For umbilical-artery catheters (UACs) the ideal anatomical location for the tip is in the descending aorta above the level of the diaphragm and below the left subclavian artery.[8, 9, 14, 15] Several formulas and graphs based on various body measurements have been proposed to predict the insertion length of umbilical catheters (see Figure 1 and 2).[16-29] The methods used for UVCs are presented in Table 1 and the methods for UACs in Table 2.

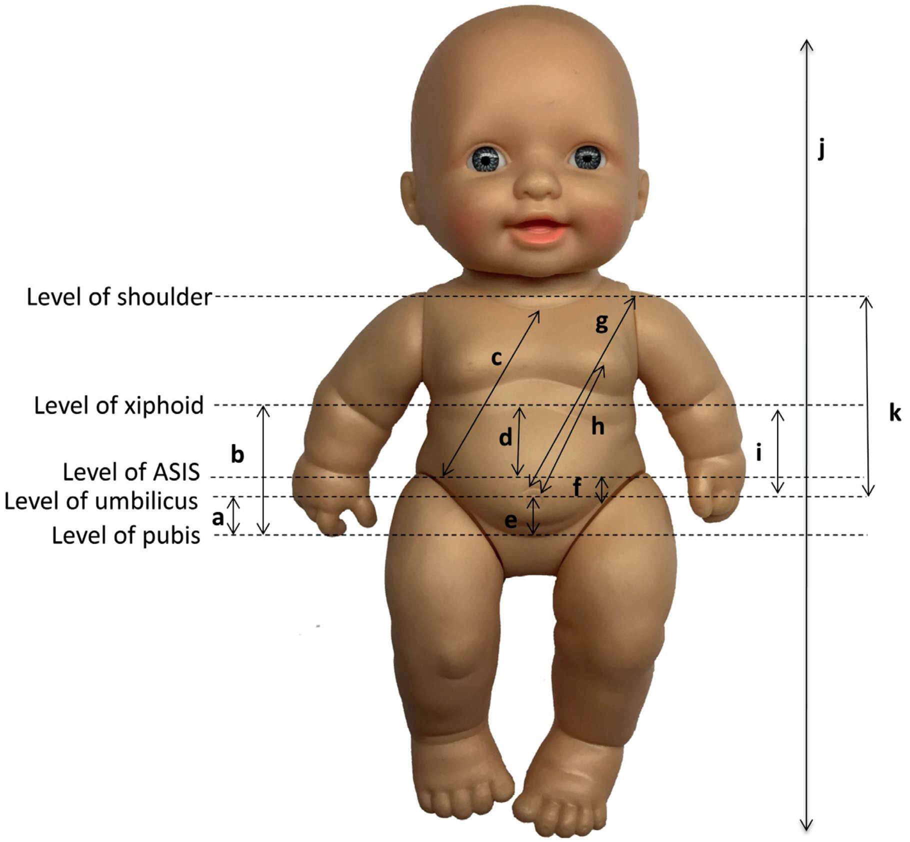

Figure 1. Different body measurements used in different methods to predict the insertion length of umbilical catheters, anterior view. a: umbilicus to symphysis pubis; b: xiphoid to pubis; c: suprasternal notch to superior iliac spine; d: xiphoid to anterior superior iliac spine (ASIS); e: umbilicus to pubis; f: umbilicus to ASIS; g: umbilicus to acromioclavicular joint; h: umbilicus to nipple; i: umbilicus to xiphisternum; j: total body length or heel-to-crown length; k: shoulder-umbilicus length;

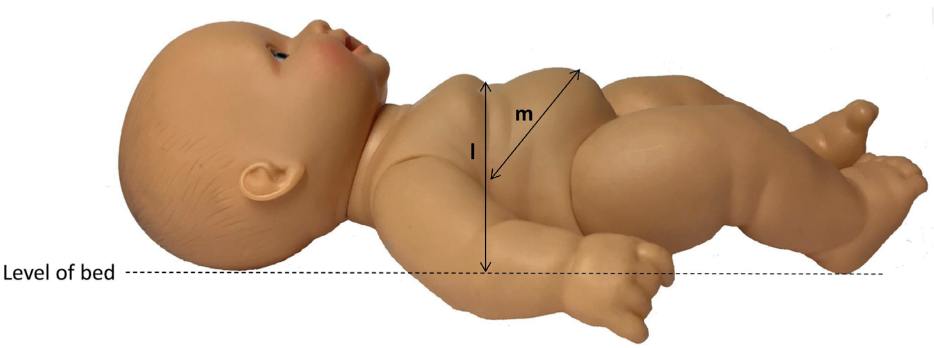

Figure 2. Different body measurements used in different methods to predict the insertion length of umbilical catheters, lateral view. l: xiphoid to bed distance; m: umbilicus to mid-xiphoid to bed distance;

Table 1. Methods to estimate umbilical venous catheter insertion length[16, 17, 22-25]

Author (year)	Short description
Dunn (1966)	Nomogram based on shoulder-umbilicus length (k)
Shukla (1986)	(3xweight (kg)+9)/2+1
Vali (2010)	Measurement from the umbilicus to the mid-xiphoid-to-bed distance on the lateral aspect of the abdomen (l,m)
Gomella (2013)	Distance from umbilicus to xiphisternum+1 cm (i)
Verheij (2013)	(3xweight (kg)+9)/2
Gupta (2015)	Distance from umbilicus to nipple-1 cm (h)

The letters between brackets refer to the relevant body measurements shown in Figure 1 and 2.

Table 2. Methods to estimate umbilical artery catheter insertion length[16-22, 25-29]

Author (year)	Short description
Dunn (1966)	Nomogram based on shoulder-umbilicus length (k)
Weaver&Ahlgren (1971)	0.33xheel-crown length (j)
Rosenfeld (1980)	Nomogram based on total body length (j)
Pollack (1981)	Shoulder-umbilicus length+weight to the nearest higher 0.5 kg (kg)
Shukla (1986)	(3xweight (kg)+9)
Rubin (1986)	Distance from xiphoid to pubis+distance from pubis to umbilicus (b,e)
Lin (1989)	For 1000 g infant, insertion length is 10 cm. Add 1 cm for each additional 250 g. Above 2250 g, insertion length is 15 cm.
Sritipsukho (2007)	Distance from suprasternal notch to superior iliac spine (c)
Wright (2008)	4xweight (kg)+7
Vali (2010)	1.1x(distance from xiphoid to anterior superior iliac spine+distance from umbilicus to anterior superior iliac spine)+1.6 (d,f)
Gupta (2015)	Distance from umbilicus to nipple minus 1 plus twice the distance from umbilicus to symphysis pubis (h,e)
RWH (Lean) (2018)	Distance from umbilicus to acromioclavicular joint (g)

RWH, The Royal Women's Hospital; The letters between brackets refer to the relevant body measurements shown in Figure 1.

The two most widely used methods are Dunn[16] and Shukla.[17] The Dunn method is based on measurement of the shoulder-umbilicus length (S-U length), and uses nomograms to determine the insertion length of the catheter.[16] Dunn defined the S-U length as 'the distance between the top of the shoulder over the lateral end of the clavicle and a point vertically beneath it that was level with the centre of the umbilicus'. However, as reported in our questionnaire (**Chapter 2**), only 14% of the neonatal caregivers in The Netherlands measured the S-U length correctly according to this definition.[30] Most respondents measured the S-U length as the distance between the top of the shoulder over the lateral end of the clavicle and the centre of the umbilicus. Following Pythagoras's theorem, measuring the S-U length in this way will lead to a deeper insertion length, and increases the possibility of a malposition of the catheter. A study by

Ades et al. showed that Dunn's method often led to overestimation of insertion length of umbilical catheters.[31] We observed that this overestimation may be partly due to incorrect measurement of the S-U length. Moreover, obtaining accurate body measurements may be difficult because of the increased flexor tone of the infant. It is also possible that caregivers do not take the time to accurately interpret the graphs needed to correlate their measurements with the positioning of umbilical catheters.

The use of equations based on birth weight, such as those developed by Shukla, may be more accurate since these methods are based solely on calculations without the need for measurement and interpretation.[17] Shukla tested these equations in a prospective study and concluded that all catheter tips were in acceptable positions. They aimed to position the tip in the inferior vena cava or right atrium, however, which is no longer recommended practice.[5, 32]

In **Chapter 3** of this thesis we assessed the accuracy of both the Dunn and Shukla methods to predict the appropriate insertion length of UACs and UVCs.[33] The overall accuracy of both methods is poor, frequently leading to umbilical catheters being positioned too high. For UACs, the Shukla method was more accurate in determining the correct insertion length and is therefore advisable. For UVCs, the Dunn method produced better results. Combining these two different methods, however, may lead to confusion and mistakes. We therefore revised Shukla's method for UVCs and validated this in a group of 92 infants (**Chapter 4**).[24] The use of this revised formula reduced the rate of over-insertion of UVCs without increasing the risk of more UVCs being placed too low. This revised formula [(birth weight x 3 + 9)/2] has the potential to reduce the rate of complications by reducing over-insertion. The formula is a derivative of Shukla's formula used to predict the insertion length of UACs [birth weight x 3 +9]. An additional advantage of these formulas is that they are easy to remember, and the simplicity minimizes the risk of miscalculation.

The Dunn, Shukla, and other methods have been compared in earlier studies (see Table 3 and 4).[25, 34-37] Different conclusions were drawn, probably due to the variations in study design.

Table 3. Comparison of methods used to predict the correct insertion length of umbilical venous catheters [24, 25, 33-36]

Author (year)	Methods compared	Ideal position of UVC on X-ray	Conclusion
Verheij (2010)	Dunn, Shukla	Th9-Th10	Dunn most accurate
Verheij (2013)	Shukla, revised Shukla	Th9-Th10	Revised Shukla most accurate
Kieran (2015)	Dunn, Shukla	Th9-Th10	No difference
Gupta (2015)	Shukla, Gupta	At diaphragm±0.5 cm	Gupta most accurate
Mutlu (2017)	Dunn, Shukla, revised Shukla	Th9-Th10	No difference, trend to Shukla most accurate
Lean (2019)	Dunn, Shukla, Vali, Gomella, revised Shukla	At or up to 1 cm above diaphragm on lateral X-ray	Gomella highest predicted success rate, Shukla most practical (highest rate of either correct or high position)

UVC: Umbilical venous catheter

Table 4. Comparison of methods used to predict the correct insertion length of umbilical artery catheters [19, 25, 29, 33, 34, 37-39]

Author (year)	Methods compared	Ideal position of UAC on X-ray	Conclusion
Rosenfeld (1981)	Dunn, Rosenfeld	L3-L5	Rosenfeld most accurate
Wright (2008)	Dunn, Wright	Th6-Th10	Wright most accurate (in VLBW infants)
Verheij (2010)	Dunn, Shukla	Th6-Th10	Shukla most accurate
Kumar (2012)	Shukla, Wright	Th6-Th10	No accurate formula for all gestational age groups. Wright less repositioning in VLBW infants.
Kieran (2015)	Dunn, Shukla	Th6-Th10	Shukla most accurate
Min (2015)	Dunn, Wright	Th6-Th10	Wright most accurate
Gupta (2015)	Gupta, Shukla, Wright	Th6-Th10	Gupta most accurate
Lean (2018)	Dunn, Shukla, Wright, Weaver&Ahlgren, Sritipsukho, Rosenfeld, Pollack, Rubin, Lin, Vali, RWH guideline	Th6-Th10	RWH guideline, Weaver&Ahlgren, Sritipsukho highest predicted success rates

UAC: Umbilical artery catheter; RWH: The Royal Women's Hospital

These different conclusions emphasize the unreliability of formulas and body measurements to predict the insertion length of umbilical catheters. Body proportions are not exactly the same in all infants or groups of infants; each person is unique. This is probably the most important reason why no one universal method can correctly predict the insertion length of catheters in all infants. Until now, no method or formula has been proven to reliably predict the correct insertion length of umbilical catheters in different gestational age and birth weight groups. However, the need for an estimation method remains and choices have to be made about which method to use in clinical practice.

Some methods use one or more body measurements in combination with calculations.[18, 22, 23, 27] However, we have demonstrated (**Chapter 2**) that body parts can easily be measured inaccurately and thus lead to inaccurate estimates.[30] The use of different measurements or patient parameters for UVC and UAC, e.g. shoulder-umbilical length for UVC and birth weight for UAC, can also easily lead to confusion. In a busy department and in situations where acute care is needed, methods based on different body measurements and complex calculations may be too demanding and possibly lead to miscalculations or misinterpretations. We therefore recommend the use of a simple method without complex body measurements or combined calculations.

In order to ensure that the inserted part of the UVC remains sterile, UVCs that have been positioned too low should not simply be repositioned. Instead, they must be removed and the procedure must start again.[36] When a UVC is positioned too high it can easily be pulled back into the correct position, although even a short period of this malposition increases the risk of complications such as cardiac arrhythmias and intracardiac thrombosis.

A catheter placed too high may cause complications, but it can be repositioned; a catheter placed too low, however, must be completely removed. For this reason, most caregivers would rather accept the risk of placing the catheter too high, and prefer a method or formula with the smallest risk that the UVC could be placed too low. This is why Lean et al. recommend the Shukla method for UVCs, although Gomella's method had the highest predicted success rate in their study.[36] In our department, the revised Shukla formula is still recommended in our guidelines for estimating the insertion length of UVCs as this method leads to less over-insertion (**Chapter 4)**. However, in practice, caregivers are anxious about UVCs being placed too low and frequently add a little length (approximately 1 cm) to the estimate during insertion, thus unintentionally reintroducing Shukla's original formula. In these situations caregivers should be especially aware of signs of the catheter-tip entering the right atrium, such as arrhythmia, and immediately pull the catheter back to prevent complications.

Practical recommendations for the positioning of umbilical catheters

- Use a method based on the same body measurement or patient parameter to predict the insertion length of both the UVC and the UAC.
- Use a simple method.
- Keep to the definition described by the author of the method and transmit this definition clearly to new colleagues.
- Whatever method is chosen, be alert to signs that the UVC or UAC may have been placed too high during catheterization and, if necessary, pull the catheter back immediately.

B) METHODS TO CONFIRM THE CORRECT POSITION OF UMBILICAL CATHETERS

Checking the position of the tip of umbilical catheters after placement is strongly recommended to prevent malpositioning. Despite attempts to position catheter tips in the appropriate location, they are often positioned too low or too high along the catheter route or are malpositioned in vessels branching off the catheter route.[9, 40-42] In the past a radiographic examination - an anteroposterior and lateral thoraco-abdominal X-ray - was used to confirm the correct position of umbilical catheters and differentiate between umbilical artery and venous catheters.[2, 3, 40, 43] More recently the value of the lateral view has been called into question, and it is now only recommended by some authors when the catheter position is still unclear after the routine anteroposterior radiograph.[6, 44] The diaphragm, the cardiothymic silhouette, and the thoracic vertebrae are used as landmarks to determine the umbilical catheter position (Figure 3). For UVCs, the position of the tip should project above the diaphragm, outside the cardiothymic silhouette and at the level of the eighth to ninth or ninth to tenth thoracic vertebra.[2, 4, 8, 31, 45] Interpretation

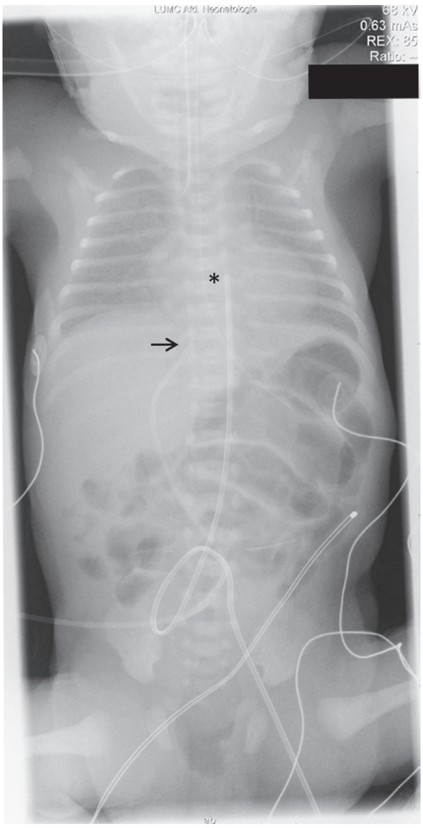

Figure 3. Anteroposterior thoraco-abdominal X-ray to determine position of umbilical catheters. The tip of the umbilical venous catheter (arrow) projects in between 9th and 10th thoracic vertebra, outside the cardiothymic silhouette, just below the diaphragm. The tip of the umbilical artery catheter (asterisk) projects just above 7th thoracic vertebra. Both catheters were accepted for use.

of radiographs including position of the catheter tip relative to the cardiac silhouette, appear to be more sensitive and accurate in assessing the position of the UVC tip than interpretation of radiographs relying solely on vertebral level.[46]

UACs in a high position are accepted when the tip is seen at the level of the fifth or sixth to ninth or tenth thoracic vertebra, and in low position when the tip is between the third and fourth or fifth lumbar vertebra.[3, 4, 9, 10] For UACs the use of bony landmarks on chest X-ray to map the location of the catheter tip with respect to vascular structures appears to be satisfactory.[8, 47] However, the desired location of the IVC-RA junction for UVCs is frequently inconsistent with these landmarks on radiographs.[8, 31, 48] Other methods have therefore been researched to give a more reliable representation of the real location of the UVC tip.

Correct positioning of the UVC can also be achieved by advancing the catheter until the electrocardiogram (ECG) has tall P-waves and QRS-complexes and then withdrawing the catheter until the P-wave returns to normal size.[49, 50] However, the effectiveness and feasibility of this technique has not been studied extensively in larger groups of patients and ECG guidance is not yet commonly used in UC. Moreover, using this method involves deliberately introducing the catheter too high in order to induce ECG changes, and this carries a risk of complications.

The most promising method to check the position of umbilical catheters is ultrasonography (Figure 4).

The first report of the use of ultrasonography to localize intravascular catheters in children, including umbilical catheters, was published in 1981.[51] One year later George et al. confirmed that using ultrasonography to establish the position of UVCs is simple and rapid, delivers no ionizing radiation, and is superior to radiographic examination in localizing UVC tips.[47] Later authors have also compared ultrasonography and radiographic examination. Most reported low correlation between thoracic level of the UVC tip and catheter location by radiographs and recommend ultrasonography,[31, 48, 52-58] although one more recent study found high agreement between radiographs and ultrasonography.[13]

In **Chapter 5** of this thesis we also compared ultrasonography and chest X-rays as methods of detecting malposition and migration of UVCs, although this was not the primary aim of the study.[59] We found disagreement concerning position in 23% of imaging pairs. When the UVC passes through the ductus venosus, it travels in both a caudocranial and anteroposterior direction. Measurements taken on digitalised anteroposterior chest X-rays represent the distance in only one plane and this may lead to misinterpretation of the tip position.[46] With ultrasonography it is possible to perform dynamic views of the catheter tip from different angles, thus leading to more accurate tip localization.[13] Other advantages are quicker, clearer results and prevention of additional exposure

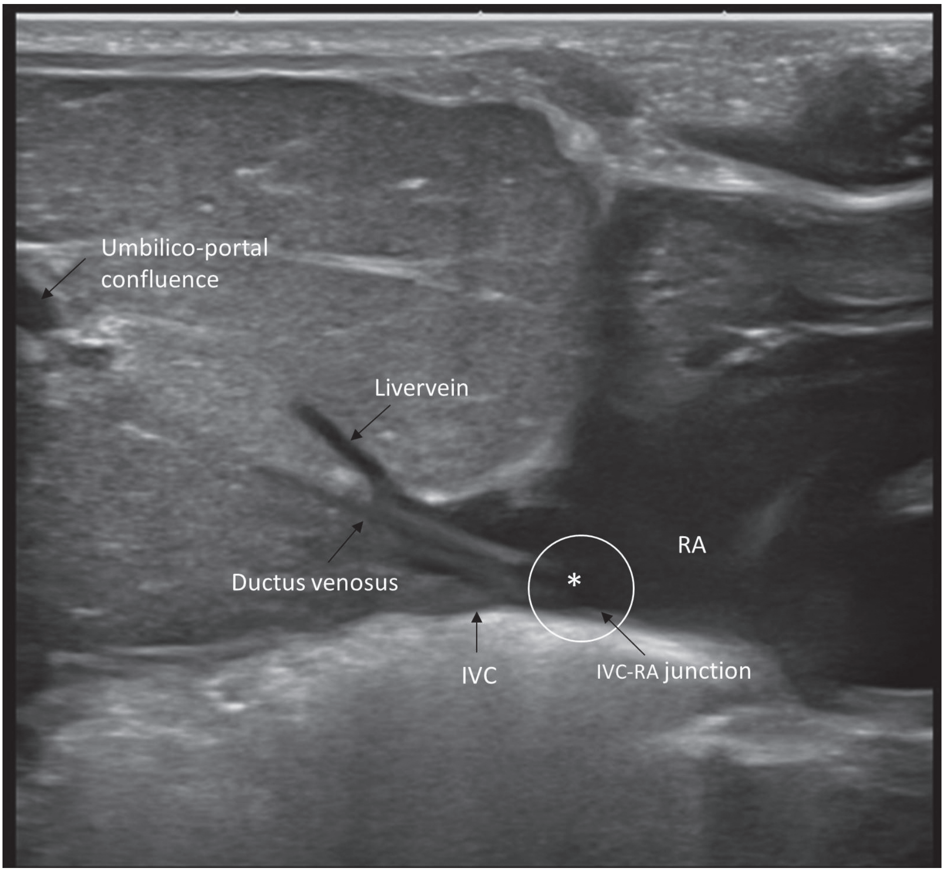

Figure 4. Ultrasound image of an umbilical venous catheter with correct position of the tip (asterisk). The tip of the catheter is localized at the junction of the inferior vena cava (IVC) and right atrium (RA).

to radiation.[13, 55, 60] Ultrasonography can be used to evaluate and guide UVC position immediately, unlike an X-ray.[61] Ultrasonography during UC decreased the time needed to place the catheter, the number of manipulations of the catheter, and the number of X-rays; it may also limit the risk of complications.[61]

Ultrasonography may be used during or directly after catheterization and also when the catheter is in place, to follow the UVC tip position over time.[13] In **Chapter 5** we reported migration of UVCs in 63% of infants. Migration of UVCs is also described in other studies, most of which reported the highest amount of migration in the first two or three days after placement, in agreement with our own observations.[54, 59, 62, 63] We found that migration frequently led to malposition.[59] To detect migration, especially migration leading to a potentially dangerous position in the heart, we now recommend confirming the position of UVCs with ultrasonography at least once, preferably 24-48 hours after placement. Few studies showed that neonatal caregivers are, after training, able to interpret UVC tip position with high accuracy rates when compared with cardiologists or radiologists.[13, 58] Ideally, UVC tip position should be checked daily in every infant, but incorporating daily ultrasonography into care at the Neonatal Intensive Care Unit (NICU) has several practical and logistical implications. Firstly, it requires some investment of time to train the clinicians to reliably detect the position of the catheter tip using ultrasound examination. Secondly, trained clinicians need to be available 24 hours a day and 7 days a week. Despite the logistical challenges, the use of frequent ultrasonography in infants with UVCs could prevent complications caused by the malposition of catheters and improve care in this vulnerable population. Efforts should therefore be made to achieve these goals.

UAC tips can be detected more reliably than UVC tips using chest X-rays. Similarly to Fleming et al.,[61] we found during the study periods that UAC tips can easily be detected with ultrasonography as well. The reliability and feasibility of ultrasonography for localizing UAC tips in comparison with chest X-rays is still unclear as no comparative studies have been performed. However, we hypothesize that, in an infant with both arterial and venous umbilical catheters inserted, ultrasonography will detect both catheter tips, making a chest X-ray obsolete.

Practical recommendations for determination of the position of umbilical catheters

- Use ultrasonography as first choice modality to determine the umbilical catheter tip position.
- If equipment is available but clinical experience is lacking: invest in training for neonatal clinicians to learn the technique of checking the umbilical catheter tip position using ultrasonography.
- If ultrasonography is not feasible: use anteroposterior thoraco-abdominal X-ray, including assessment of the catheter tip in relation to vertebral level, diaphragm and cardiothymic silhouette to determine tip position. If in doubt, add lateral X-ray.
- Re-evaluate the UVC tip position when in place, preferably using ultrasonography, and at least once 24-48 hours after placement.

C) COMPLICATIONS ASSOCIATED WITH UMBILICAL CATHETERIZATION

Despite efforts to achieve and maintain the correct position of umbilical catheters, complications during and after UC cannot be totally avoided. In this thesis, we have described the occurrence of several possible complications of umbilical venous catheterization, including hypothermia (**Chapter 6**), cardiac arrhythmias (**Chapter 7**), thrombosis (**Chapters 8 and 9**) and bloodstream infection (**Chapter 10**). Most complications are not only related to UVCs but also to other central venous catheters (CVCs), such as femoral venous catheters (FVCs) and peripherally inserted central catheters (PICCs). In **Chapter 9** and **Chapter 10** of this thesis we therefore compared the incidences of thrombosis and bloodstream infection between UVCs, FVCs and PICCs.

Hypothermia

Hypothermia in infants is associated with increased neonatal mortality and morbidity and must be avoided.[64-69] During the first 'golden hour' of premature life, procedures such as UC are performed to stabilize the infant as soon as possible.[70, 71] However, these procedures may cause or contribute to the development of hypothermia. As described in **Chapter 6** of this thesis, hypothermia already existed in 69% of infants in our NICU before the start of UC, and increased to 89% during the procedure. To our knowledge, no other studies investigate the whole course of the temperature of infants during UC. In our study a decrease in temperature was observed at the start, with temperature stabilizing and sometimes rising again in the latter part of the procedure. This is the most likely explanation why the duration of the procedure was not associated with temperature decrease or hypothermia.

The high proportion of infants with hypothermia at the start of UC in our department is alarming, and it is important to optimize the prevention of heat loss after birth. Performing UC in these hypothermic infants may lead to inadequate rewarming and may even decrease their temperature further. We recommend postponing this procedure until the infant's temperature is normal, unless it is impossible to give the infant alternative, more quickly inserted, intravenous access during waiting time. In hypothermic infants, UC is not essential and may even be a harmful step in the first 'golden hour' of life.

Practical recommendations concerning hypothermia

- Verify the temperature of the infant before the start of UC.
- In case of hypothermia: give alternative (temporary) intravenous access and postpone UC, even during the 'golden hour', until the infant is rewarmed.
- During UC: measure skin temperature continuously and take measures to prevent hypothermia during the procedure.

Cardiac arrhythmias

Cardiac arrhythmias are a known complication of UVCs.[1, 4, 5] Mechanical irritation of the atrium or mechanically induced premature atrial beats may be the initiating triggers for atrial flutter or for supraventricular tachycardia (SVT) in the presence of an accessory atrioventricular myocardial pathway.[72, 73] In infants without UVCs a newly developed tachyarrhythmia is usually caused by a SVT, and atrial flutter is almost exclusively observed in fetal life or immediately after birth.[74] However, in **Chapter 7** we described that in 6 out of 10 cases of cardiac arrhythmias related to UVCs the cause of the arrhythmia was an atrial flutter.[72] Atrial flutter is therefore a more prominent cause of tachyarrhythmia in infants with UVCs than in those without. Awareness of the possible types of arrhythmia is necessary, because distinction of the type is critical to guiding treatment.

In all cases described in our literature review, the UVC was assessed as too high by chest X-ray or ultrasonography. Not much is known about the incidence of cardiac arrhythmias related to UVCs. After the publication of our case study, three other case reports of a SVT (n=2) and atrium flutter (n=1) were published.[73, 75, 76] In one of these cases the arrhythmia developed 30 hours after placement of the UVC and migration of the catheter to malposition was demonstrated.[75] Interestingly, in the last case multiple doses of adenosine were not successful in treating the SVT until the catheter was withdrawn. All cases emphasize the risk of UVCs positioned with the tip in the heart and the importance of evaluation and re-evaluation of UVC position as is also discussed in **Chapter 5** of this thesis.[59]

Practical recommendations concerning cardiac arrhythmias

- Prevent the UVC being positioned too high or limit its duration as much as possible.
- The first step to treat cardiac arrhythmias in an infant with a UVC should be to pull back or even remove the UVC.
- If pulling back the catheter is not successful: use the normal treatment according to the type of arrhythmia (vagal response and adenosine in SVT, synchronized cardioversion or transoesophageal pacing in atrial flutter).

Thrombosis

The most common risk factor for neonatal thrombosis is catheterization of the central veins or arteries.[77, 78] In the study described in **Chapter 8** we prospectively screened for thrombi along the entire UVC route and detected a high incidence of 75%. The incidence of thrombosis reported in the literature is lower than in our study and varies greatly from 2.2% to 43%.[79-86] The lower reported incidences in previous studies may be due to the retrospective study design or the fact that only one part of the UVC route was evaluated. We assessed the presence of thrombi along the whole UVC route and found thrombi in a wide variety of locations, including umbilico-portal confluence, ductus venosus, junction of ductus venosus and inferior vena cava/right atrium and right atrium (Figure 5).

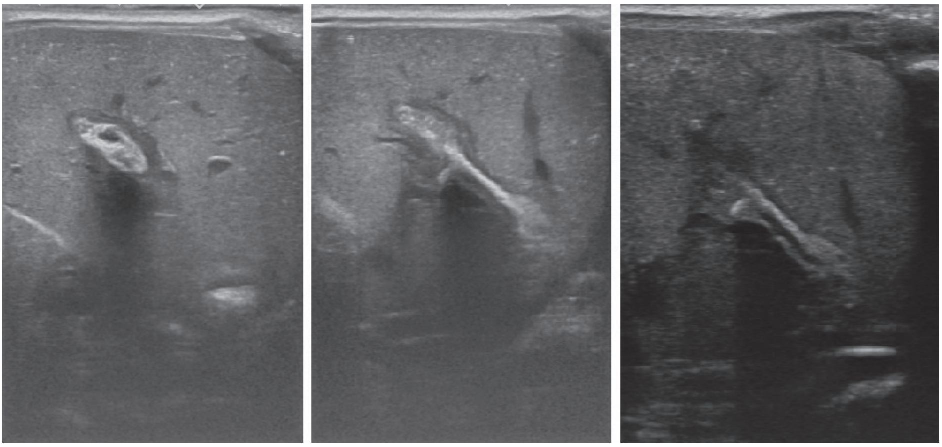

Figure 5. Premature infant with gestational age 31 weeks, 1415 grams. Thrombus in umbilico-portal confluence and ductus venosus. Images performed at day 8 after catheterization, before and after removal of UVC. First two left images with UVC still in situ. Right image: after removal of UVC a linear hole is observed within the thrombus.

Ours is the only study to date that includes a control group of infants without UVCs. Thrombus formation has been suggested as contributing to the physiological process of closure of the ductus venosus.[87, 88] However, a thrombus was not detected in any of the infants in our control group (**Chapter 8**).

Only a few studies, all with a much smaller study population, compared the risk of thrombosis in the different catheter types used in neonates.[85, 89-91] In our retrospective study in a cohort of infants born at 34 or more weeks' gestation (**Chapter 9)** we reported a higher incidence of clinical thrombosis in FVCs compared with UVCs and PICCs.[92] One other study also reports a higher incidence in infants with FVCs compared to UVCs.[85] In accordance with our study, previous retrospective studies report similar incidences of thrombosis in infants with PICCs and UVCs.[90, 93]

The clinical significance of thrombi detected by routine screening is debatable and controversial. Current management varies greatly from expectant management to aggressive thrombolytic therapy. However, there is little data concerning the long-term consequences of these thrombi, and current guidelines are mainly based on expert opinion.[90, 94-96] Most centers do not advise routine screening for thrombi in all infants with UVCs. Currently, a large multi-center prospective observational cohort study is being carried out in the Netherlands to evaluate the efficacy and safety of the national neonatal central venous catheter-thrombosis guidelines and to analyse the risk factors and long-term consequences of central venous catheter-thrombosis (Neoclot study).[97]

Ultrasonography is increasingly used at the NICU by neonatologists for multiple reasons other than screening. As a result, given the high frequency of thrombus formation observed in our population, detection of thrombi will also increase. The optimal management for catheter thrombosis is controversial and not well known. Some authors advise removing a catheter once a thrombus is detected, unless the catheter is vital for the survival of the infant or for administering thrombolytic therapy,[5, 96] while others opt for a "wait and see" approach. Our study showed that spontaneous resolution of UVC-related thrombi is likely to occur (**Chapter 8**). Until the results of the Neoclot study are published we would advise removing the UVC only in the case of clinical symptoms, such as persistent thrombocytopenia without other explanation. In asymptomatic thrombi detected accidentally or through routine screening the UVC may stay in place with close monitoring, but needs to be removed in case of growth of the thrombus or development of new clinical symptoms related to thrombosis. Importantly, in infants with UVCs, longer catheter dwell time (>6 days) was associated with a higher risk of portal venous thrombosis.[80] For this and other complications it would be best to use UVCs for the shortest time possible.

Practical recommendations concerning thrombosis

- Do not routinely screen for thrombosis in all infants with UVCs.
- To avoid complications: always remove UVCs as soon as the catheter is no longer needed.
- If thrombosis is found and CVC is still needed: remove catheter only if clinical symptoms are present.

Bloodstream infection

Bloodstream infection is a common complication of all CVCs, including UVCs. In our cohort study the incidence of central line-associated bloodstream infection (CLABSI) was 5.7% in UVCs compared with 4% in PICCs and 8% in FVCs (**Chapter 10**).[98] Although a trend towards a higher CLABSI incidence in FVCs was observed, there was no statistical difference. Other studies that have compared the risk of CLABSI in different catheter types draw conflicting conclusions.[85, 91, 99-104] Differences in CLABSI incidences between different CVCs found in some studies may not be caused by the type of catheter but by differences in the selection of infants who receive a specific catheter type. The clinical context, with differences in care during and after insertion, may also play an important role.[105] Emphasizing hand hygiene, using bundles of care, and training a dedicated team to insert CVCs have been proven to reduce the incidence of CLABSI.[106-109]

Some NICUs advise a maximum UVC dwell time of 7 days to prevent catheter-related infections. However, the evidence suggesting that a dwell time <7 days reduces the risk of infections compared to > 7 days, is weak.[79, 110, 111] In infants using UVCs for up to 14 or 28 days, reported incidence of bloodstream infection was similar to that of infants with peripheral lines only or a UVC followed by PICC after 7-10 days.[79, 111] Some authors suggest replacing the UVC with a PICC after the first days of use based on an increasing risk of CLABSI within the first week after insertion.[105, 112] However, there is little solid evidence to support this advice; applying the same hygiene guidelines during and after catheterization in all catheter types is probably more important than changing a specific catheter after a few days. Moreover, a recent retrospective study comparing CVC-related complications between umbilical and non-umbilical catheters reported a higher incidence of complications (including CLABSI, pericardial effusion and tamponade) in non-umbilical catheters when compared to umbilical catheters.[113]

Practical recommendations concerning bloodstream infection

- Implement strict hygiene guidelines and specific care bundles to use during and after UC.
- Use checklists to help physicians apply these guidelines.
- Each NICU should routinely evaluate and benchmark the incidence of catheter-related bloodstream infection to detect fluctuations and strive towards reducing infections.

Balancing risks versus benefits of umbilical catheters

The risks of complications associated with UVCs should always be balanced against their numerous practical benefits. UVCs provide easy and rapid intravenous access and UC can be easily taught to inexperienced caregivers at the NICU. Importantly, in infants with a UVC during the first period of life, less time and money are spent obtaining peripheral line placement and less painful venipunctures are necessary.[111]

Over the past decade an increasing amount of research has led to an improved knowledge on the potential complications of UVCs. Oelberg et al. report no benefit of successful UC in extremely premature infants with respect to reduction of mortality and morbidity when compared to unsuccessful UC,[114] and reported a higher survival rate in infants without a UVC. Elborae et al. also report an association between the presence of umbilical catheters and adverse outcome (mortality or major neonatal morbidity).[115] However, both studies have a retrospective design and, although adjustment for confounders was performed, the results were most probably limited by selection bias. A causal association between UVC and mortality or morbidity could not therefore be proven.

UVCs share many complications with other CVCs. This raises the question of whether there is one type of CVC with the lowest complication risk. Some physicians and authors are startled if confronted with threatening complications, such as cardiac tamponade, and become hesitant to use UVCs or even discourage their use.[116] However, cardiac tamponade and pericardial effusion are described in other types of CVCs as well, apparently with similar incidences.[117, 118] In our NICU, with infants in need of a CVC, we generally choose between insertion of a UVC or a PICC. FVCs are less likely to be an option, because a large part of our population has a low birth weight and/or gestational age and neonatologists at our department are not experienced in the insertion of FVCs. Taking into account the results of our studies reported in **Chapters 9** and **10** and the conflicting results of other studies published until now and discussed in this thesis, there seem to be no grounds for discouraging the use of UVCs in infants needing a CVC. Migration of the catheter may increase the risk of serious complications, such as cardiac tamponade, but is reported in PICCs as well.[118-120] This phenomenon therefore cannot support preference for one type of CVC over another.

Although no clear differences exist between complications according to the different CVC types used, physicians should be aware that the use of any CVC, irrespective of its type, may cause severe morbidity. In light of this knowledge, we should always think twice before inserting a CVC in a preterm infant. Guidelines have now been developed to standardize the use of umbilical catheters.[121] These and similar guidelines are implemented at NICUs all over the world to select patients who will benefit and to prevent the overuse of CVCs, including UVCs.

In conclusion, UC is an excellent method for gaining intravenous access in sick infants, especially in extremely premature infants with small and fragile vessels and in infants with haemodynamic instability. The use of UVCs in all infants should therefore not be excluded and the advantages should not be underestimated. However, as in other CVCs, complications cannot always be avoided. This leads to a so-called 'love-hate relationship' between neonatologists and UVCs. Caregivers using UVCs must be able to critically assess the necessity of insertion of a CVC. Then, if the UVC has been inserted, they must remember the essential components of good care: awareness of potential complications, quick evaluation of symptoms that indicate complications, and regular re-evaluation of the position of the catheter and the continued need for its use.

General practical recommendations

- Critically weigh up the necessity of insertion of a UVC with its potential complications before performing UC.
- Be aware of the possible complications related to the use of UVCs and pay attention to potential symptoms of catheter-related complications.
- Regularly re-evaluate the position of the UVC.

FUTURE PERSPECTIVES

Since the first report on UC in 1948 many studies have followed, and the procedure is now common practice at the NICU. However, more knowledge is still needed about the optimal method of inserting catheters in the correct position, how to confirm correct position in daily practice, and the benefits and risks of umbilical and other central catheters.

A) Methods to predict correct insertion length of umbilical catheters

Despite decades of research, the optimal formula or method to predict the correct insertion length of umbilical catheters has not yet been determined. A more accurate formula or method to determine the optimal insertion length is urgently needed, particularly in healthcare situations with no ultrasonography or even radiology available. To develop such a formula, prospective studies using ultrasonography to collect ideal insertion lengths of UVCs in different patient groups must be performed.

B) Methods to confirm the correct position of umbilical catheters

Use of ultrasonography must become more widespread among neonatologists. In analogy to cranial ultrasonography, routine ultrasound examination of the position of central catheters, including umbilical catheters, should be incorporated into daily NICU practice. To reach this goal, neonatologists must be given basic training to carry out targeted neonatal cardiac and abdominal ultrasonography. Moreover, trained clinicians need to be available 24 hours a day and 7 days a week. The feasibility of this implementation in NICUs in the Netherlands therefore needs to be evaluated. Equipment costs and availability of caregivers have to be balanced against the expected benefits of less malposition (and complications) and decreased duration of the procedure in a cost-effectiveness analysis. Furthermore, while UAC tips can easily be detected by ultrasonography, studies to compare ultrasonography with chest X-rays in terms of feasibility and reliability to detect UAC tips are also needed .

C) Complications associated with umbilical catheterization

To determine the benefits and risks of UVCs in comparison with the alternatives, such as a PICC or no CVC at all, and to evaluate the association with mortality and morbidity in (preterm) neonates, randomized controlled trials (RCTs) are needed. In these trials infants should be randomized to a UVC, a PICC, a UVC followed by a PICC, or no CVC at all. These studies should also evaluate the effect of different timing of insertion (directly after birth versus a few hours or days afterwards, or later placement based on clinical need). Mortality, incidence of complications such as bloodstream infection and thrombosis, infant temperature, impact on the patient, and investment of time by the physician should all be evaluated. It is essential to develop an improved knowledge of the risks and associations of migration of UVCs as well as PICCs. Finally, more studies (ideally RCTs) are needed to evaluate the benefits and risks of UACs compared to peripheral artery catheters or no artery catheter at all.

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