# Neonatal pearls : safety and efficacy of medication use in fetus and neonate

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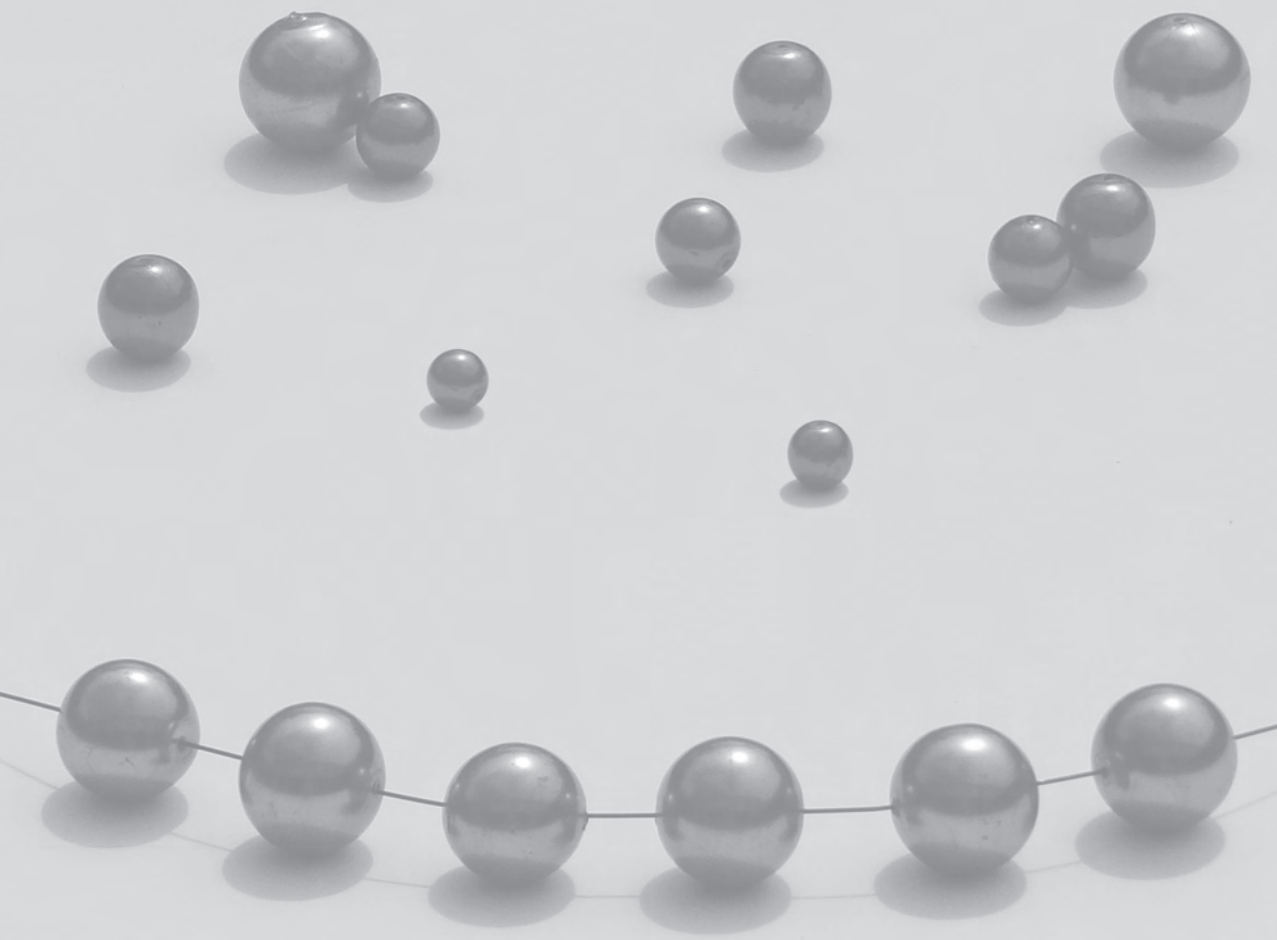
# Chapter 8

# General discussion



# Introduction

In this chapter we will discuss each "pearl" separately, provide short recommendations for best practice and future perspectives.

## Lithium: Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies

Since 1970 lithium is registered by the Food and Drug Administration for treatment of acute manic episodes and as maintenance treatment for patients with bipolar disorders. Question rose about the safety of lithium during pregnancy for the developing fetus, as bipolar disorders are common in women of childbearing age.[1] An international register of lithium babies, consisting of 225 infants exposed to lithium during pregnancy, reported an extremely increased risk (500-fold) for Ebstein's anomaly. Ebstein's anomaly is a very rare cardiac malformation with an incidence of 1:20.000 in normal pregnancies.[2] Since that reported outcome, lithium was considered teratogenic and usage during pregnancy was highly dissuaded. Later case-control and cohort studies showed the 500-fold increased risk to be overestimated, due to a voluntary reporting bias of the lithium baby register. A causal relationship between intra-uterine lithium exposure and Ebstein's anomaly could not be ruled out, as a general incidence of 1:20.000 would require a very large study population, but other studies showed the expected increased risk to be maximal 28-fold.[3-5]

Slowly, lithium usage during pregnancy was reintroduced as the benefits of lithium continuation for maternal wellbeing became clear: discontinuation of lithium during pregnancy resulted in a 2-fold greater risk of recurrence of a new episode.[6,7] In addition, prenatal and postpartum maternal illness can have negative consequences for later neurobehavioral outcome of the infant.[8] Considering the small risk of teratogenic effects and the high risk of relapse after discontinuation of lithium during pregnancy, a balanced decision about optimal management should be made for each bipolar woman individually. Crucial information on the long term neurobehavioral outcome of intra-uterine lithium exposure is scarce. Only one other study reported the follow-up of 60 infants, but this was performed with questionnaires, which created a considerable bias.[9] The study in this thesis is the first follow-up study of lithium-babies performed by professionals using verified developmental scales. We found a normal neurobehavioral outcome in 15 infants exposed to lithium in utero. The small group size and the lack of an appropriate

control group are limitations and a much larger study population is necessary to draw more definite conclusions. While we are awaiting larger studies, these data can give counseling doctors and bipolar women more confidence in planning a safe pregnancy.

### Recommendation

Teratogenicity of lithium is relatively limited and to date no evidence of impaired neurobehavioral outcome of offspring after intra-uterine lithium exposure has been reported. Therefore, we recommend continuation of lithium therapy during pregnancy in bipolar women who have until then benefited here from. Advantages and disadvantages of continuing lithium therapy during pregnancy should be precisely balanced for each bipolar woman individually.

### Future perspectives

As lithium usage during pregnancy has slowly increased since the reports of less increased risk of teratogenicity from Jacobson and Zalstein, there must be large numbers of intra-uterine exposed infants.[3,4] Psychiatric departments are still performing studies to determine the most optimal treatment strategy of bipolar women during pregnancy and include large numbers of mothers and infants.[6,7,10] To gain more knowledge about the long term effects of intra-uterine lithium exposure it would be very helpful to add neonatal and long term follow-up evaluations to such relatively large psychiatric studies. As these mothers already consented for their own postpartum evaluation, they are probably also interested to consent for follow-up evaluation of their infant.
Importantly, future studies should include an adequate control group of infants from bipolar mothers who were not treated with lithium. As postpartum maternal illness can have influence on long term neurobehavioral development, comparison with control infants of non-bipolar mothers will not be reliable enough to demonstrate possible long term effects of intra-uterine lithium exposure.

## 8 Antenatal IVIG: Neonatal outcome in allo-immune thrombocytopenia treated with antenatal intravenous immunoglobulin

The most common cause of severe thrombocytopenia in fetus and neonate is fetal and neonatal thrombocytopenia (FNAIT).[11-13]
Maternal immunization to paternally inherited antigens on fetal platelets causes

destruction of fetal platelets and severe fetal and neonatal thrombocytopenia. This disorder is comparable with red cell allo-immunization, but in contrast to that condition, FNAIT can also affect first pregnancies. Screening for FNAIT has not been realized yet, so the first child is frequently severely affected with severe thrombocytopenia and intracranial hemorrhage (ICH), which often occurs antenatally.[14-16]

Cornerstone for the management of pregnant women, allo-immunized in a previous pregnancy, is antenatal treatment with intravenous immunoglobulins (IVIG) or, in some centers, with additional steroids. There is a rising trend towards a more non-invasive approach with minimization of fetal blood sampling, because the complication rate of this procedure (4.4-14% per pregnancy) is similar to or even higher than the risk for ICH in antenatally treated infants (0-10%).[17-24] Effectiveness and safety of a (non-invasive) policy with maternal IVIG were confirmed by studies in our center by van den Akker et al. (2007) and in the study outlined in this thesis.[21]

Questions about the optimal dosage and the best age to start IVIG remain and require further investigation. In only one study dosage was varied from 1 g/kg to 2 g/kg maternal body weight, without clear benefits for one specific dose.[23] Most studies about FNAIT report small groups and even smaller subgroups (sometimes varying in more than one study variable), making it difficult to draw firm conclusions. Because of this paucity of data, it is important to report all affected cases, as this may lead to a general international point of view and management can be based on a larger cohort of infants. Currently, a large international web-based registry of all FNAIT cases is active with antenatal IVIG dosages of 0.5 g/kg or 1.0 g/kg maternal body weight. This registry may shed more light on the optimal antenatal management in the near future.

In addition to optimizing therapy for already known affected cases of FNAIT, prevention of complications in first affected pregnancies is another important research topic. As HPA 1a incompatibility is responsible for 80-95% of the affected cases, screening for HPA 1a negative genotypes in all pregnant women is the first step in this process.[17,18,21,23,25-27] However, only 8-12% of these HPA 1a negative women with fetal incompatibility will become immunized and produce allo-antibodies.[27-32] Producing allo-antibodies is highly dependent on HLA type, e.g. HLA DRB3*0101 positivity is a poor predictor of becoming immunized, but has a high negative predictive value of 96-100%.[27,28,32] Since there are still no clear factors to predict which immunized HPA 1a negative women are at greatest risk for delivering a severely affected neonate, antenatal screening is not practical yet. Some studies suggest use of the level of maternal antibody titer during pregnancy as a possible predicting factor, but data on its predictive value are conflicting and the diagnostic value is not clear.[24,28,29]

### Recommendation

We recommend treatment of FNAIT according to a non-invasive protocol, with administration of antenatal IVIG starting at 16-18 weeks' gestation in high risk pregnancies (i.e. those with ICH in an earlier sibling) and at 28 weeks' gestation in standard risk pregnancies. Our small study does not allow us to make a statement about an optimal dosage of IVIGs and gestational age to start, although in our cohort a dose of 0.5 g/kg in standard risk pregnancies and 1 g/kg maternal body weight in high risk pregnancies seemed effective in preventing ICH.

A matched platelet transfusion should be given if the platelet value at birth is <20 x $10^9$/L in non-bleeding and <50 x $10^9$/L in bleeding infants. In case of an emergency (i.e. clinical bleeding) and no immediate availability of matched platelets, random platelets may be life-saving and recommended. When multiple matched platelet transfusions do not result in a sufficient rise in platelet value, treatment with IVIG should be considered. Neonatal platelet values need to be determined at least daily during the first days of life, until a spontaneous rise or stable level is observed.

### Future perspectives

Future research should focus on finding usable predictive factors for a neonate with FNAIT in the first pregnancy, to prevent overtreatment of all immunized HPA 1a negative women and to treat only those pregnancies at highest risk for severe FNAIT. Only when useful predictive factors have been identified, antenatal screening and selective antenatal treatment may contribute to a reduction in long term neurodevelopmental morbidity due to ICH and will become a cost-effective intervention. More knowledge about optimal gestational age to start and dosing regimen of antenatal IVIG would be very valuable to optimize antenatal treatment of already known to be affected neonates with FNAIT. Addition of long term follow-up assessments to future studies, can give more insight in possible effects of antenatal IVIG on long term neurobehavioral outcome.

## Ibuprofen: Repeated courses of ibuprofen are effective in closure of a patent ductus arteriosus.

Closure of the ductus arteriosus in term infants normally occurs within 48-72 hours after birth, stimulated by an increase of arterial pO2 and decrease of circulating vasodilating prostaglandins. In preterm infants the ductus arteriosus frequently fails

to close or remain closed, with an incidence of 55-70% in those with a gestational age of <29 weeks or a birth weight of <1000 gram. The premature ductus arteriosus has a higher sensitivity for circulating vasodilating factors, such as nitric oxide and prostaglandins, and limits vasoconstriction, hypoxia, ischemia and the process of changing into a non-contractile ligament.[33-36]

Patency of the ductus arteriosus (PDA) was associated with increased morbidity and mortality and this led in the mid 1970s to a search for adequate treatment opportunities. Based on a few small randomized controlled trials, reporting improvement of lung compliance, shorter duration of mechanical ventilation and shorter need for oxygen after surgical or pharmacological ductal closure, the main goal of management became closure of a hemodynamic significant PDA.[37-43] Since that time, a multitude of studies to detect the most optimal treatment strategy for PDA closure have been performed: fluid restriction, non-steroidal anti-inflammatory drugs (NSAIDs) which selectively inhibit cyclooxygenase and the formation of prostanoids from arachidonic acid (COX inhibitors such as indomethacin and ibuprofen), indomethacin versus ibuprofen, prophylactic versus symptomatic approach, pharmacological versus surgical closure, oral versus intravenous ibuprofen and studies to determine the most optimal dosing regimen for pharmacological closure.

However, in contrast to the short term effects on lung function, effects of ductal closure on general neonatal morbidity and neurodevelopmental outcome were only sporadically investigated. Associations of PDA with NEC and chronic lung disease were confirmed in recent studies, but causality was never proven and these complications occurred despite ductal closure.[44-49] Although a delay of surgical closure of >21 days results in a longer duration of mechanical ventilation and higher oxygen need, long term outcome such as chronic lung disease has not been reported.[50] A prophylactic indomethacin protocol prevented severe IVH, but did not influence neurodevelopmental outcome at follow-up.[51] Mortality is the only concrete outcome measure in which the benefit of ductal closure seems clear, with an odds ratio of 8 for preterm infants with failure of ductal closure.[52]

Since neonatal health care developed and improved drastically in the last 30 years (including the introduction of antenatal steroids and surfactant usage), some authors doubt the advantages of ductal closure and treatment preferences of PDA are again a hot topic. The fundamental idea that closure of a hemodynamic significant PDA is preferable is based on evidence of more than three decades ago, but it is questionable if our current population of preterm infants is comparable with the nursery population of

30 years ago. Vanhaesebrouck et al investigated a conservative approach with increase in mechanical ventilation conditions (PEEP) and decrease in daily fluid intake and found a high rate of spontaneous ductal closure. However, this study lacks data on the duration of spontaneous ductal closure, long term morbidity and consequences of a possible longer duration until ductal closure. [53] Others suggest to investigate symptomatic treatment of PDA, instead of focusing on ductal closure.[54]

A main problem in the quest to prove the possible disadvantages of ductal closure (or confirm the earlier reported benefits) is the difficulty to design an ethically justified randomized controlled trial, in which half of the PDA's will be closed and the other half will remain open. Such a RCT should include long term follow-up to assess neurodevelopmental outcome and long term consequences of neonatal morbidities such as chronic lung disease, NEC, and ROP.

Until there is evidence to demonstrate that it is better to leave a PDA untreated, studies striving for optimization of ductal closure, like the study reported in this thesis, remain necessary. We found an acceptable closure rate of PDA after a second and even third course of ibuprofen, without additional adverse effects. Based on these results we prefer a third course of ibuprofen, after a failed second course, above possible harmful surgical closure.

## Recommendation

Our current treatment policy is still focused on closure of the hemodynamic significant PDA because no disadvantages of closure have been demonstrated. Our retrospective study demonstrated that second and third courses of ibuprofen, in an attempt to close the ductus, were effective and safe. We therefore prefer multiple courses of ibuprofen above possible harmful surgical closure.

## Future perspectives

Partially based on our results, the most realistic design to gain more knowledge about the advantages and disadvantages of ductal closure (without performing a RCT) is a large scale prospective study. In this study all preterm infants with a hemodynamic significant PDA should be initially treated with ibuprofen, up to three courses if necessary. Data about mortality, morbidity, long term neurobehavioral development and long term consequences of neonatal morbidities should be collected prospectively. These outcomes should then be correlated with the duration of the PDA. Recently, two case-series of preterm infants treated with paracetamol for PDA (because of COX-inhibitor resistance or contra-indications) were published, with surprising closure

rates. Larger studies of paracetamol treated infants are needed to analyze effects and side effects of this treatment.[55,56] Another upcoming issue is the usage of oral instead of intravenous ibuprofen as cheap alternative. Also for this treatment approach more large studies are necessary to confirm the efficacy and especially the safety of oral ibuprofen, before considering this as treatment of first choice.[57-59]

## Rifampin: Use of rifampin in persistent coagulase negative staphylococcal bacteremia in neonates

Late onset sepsis (i.e. >72 hours after birth) is a common problem in Neonatal Intensive Care Units and is mainly caused by coagulase negative staphylococci (CoNS), which are considered to be minimal virulent pathogens. CoNS are skin commensals and are therefore often seen as contaminants in blood cultures. However, their presence on the skin facilitates entry into the body through indwelling catheters, which are an important risk factor for CoNS bacteremia and may present with serious illness with clinical sepsis and instability.[83-87]

Among infants with CoNS bacteremia 12-40% develops persistent CoNS bacteremia, which is in most studies defined as at least 3 positive blood cultures with the same species despite antimicrobial treatment drawn at intervals of at least 48 hours.[88-91] Risk factors for persistent CoNS bacteremia are low birth weight, low gestational age, low absolute neutrophil count (<1000 cells/μL), parenteral feeding and receiving artificial instead of breast feeding. A relationship with the persistence and presence of indwelling catheters remains doubtful, as some studies confirm and others deny this relationship.[88,90-93] Short term outcome of persistent CoNS bacteremia includes an increased incidence of neonatal hyperglycemia, endocarditis and higher creatinine levels (possibly due to longer duration of vancomycin treatment), but neonatal mortality does not increase due to persistence.[89-93] In the long term, persistent CoNS bacteremia is associated with longer hospitalization and chronic lung disease (O2 need at 36 weeks postmenstrual age).[93]

The incidence of late onset sepsis in preterm infants is increasing, possibly due to increased survival of very preterm infants and increased usage of indwelling catheters.[83,84] The incidence of persistent CoNS bacteremia is also increasing, with higher minimal inhibitory concentrations (MIC) of vancomycin to provide adequate treatment of CoNS bacteremia as well.[91,93] The cause of this increased incidence

and decreased susceptibility for vancomycin is not totally clear yet. Most likely it's a complicated process of changes in virulence of the CoNS species, colonization of the NICUs and the admission of more extreme preterm infants. An important bacterial virulence factor is biofilm production, which is more common in persistent compared to non-persistent CoNS isolates. These biofilm producing CoNS isolates (especially S. epidermidis) have increased MIC values and resistance to many antimicrobials. Another consequence of biofilm production is a reduced access of antimicrobials through indwelling catheters.[90,94-96] Hypothetically, an increase in biofilm producing CoNS species that colonize our NICU's could be explain the changes in epidemiology. However, the studies reporting an increased incidence of persistent CoNS bacteremia do not report the biofilm production of their isolates. In addition, some studies have shown that bacteremia persists after removal of indwelling catheters, suggesting that other factors than biofilm are also responsible for persistence.[89,91]

Although the complete causal pathway leading to an increasing incidence of persistent CoNS bacteremia is not clear yet, we have to deal with this serious health problem in neonatal health care. Several studies in adults have confirmed the additional value of rifampin to antimicrobial treatment.[97-101] In neonates only 16 clinical cases (and 21 cases in a pharmacological analysis) were reported before we studied a series of 18 neonates, outlined in this thesis. We confirmed the additive effect of rifampin to vancomycin treatment for persistent CoNS bacteremia, with sterilization of blood culture within 2.3 ± 1.6 days and a considerable decline of C-reactive protein (CRP), especially in the first 3 days of rifampin treatment. However, special attention should be paid to optimization of vancomycin treatment by monitoring blood levels.

## Recommendation

Based on current evidence we recommend vancomycin monotherapy when CoNS, susceptible for vancomycin, are isolated from a blood culture. Vancomycin trough and peak serum levels should be precisely monitored to optimize treatment. Indwelling catheters should be removed when blood culture becomes positive, but only if the clinical condition of the neonate does allow this. When bacteremia persists for at least 6 days, with 3 positive blood cultures (with 48 hours intervals), we recommend adding rifampin therapy to vancomycin. In addition, echocardiography and an ultrasound of the large abdominal vessels should be done to exclude an intravascular thrombus as cause of the persisting bacteremia.

### Future perspectives

To gain more knowledge about the changing epidemiology of late onset sepsis caused by CoNS, we need a prospective study with a large cohort of infants with non-persistent and persistent CoNS bacteremia, describing clinical as well as microbial and pharmacological details. In addition, it would be very valuable to compare duration of bacteremia with and without rifampin addition, in a placebo-controlled double blind randomized controlled trial. As persistent CoNS bacteremia is associated with neonatal morbidity on short term and chronic lung disease on long term, investigation of neurobehavioral outcome on long term is desirable.

## Postnatal IVIG: Outcome and management in neonatal thrombocytopenia due to maternal ITP

The incidence of idiopathic thrombocytopenic purpura (ITP), also known as auto-immune thrombocytopenia, in pregnant women is 1-10:10.000. Maternal anti-platelet antibodies, especially against GPIIb/IIIa platelet proteins on the cell membranes of all platelets, cause maternal thrombocytopenia and can pass via the placenta to the fetus.[60-63] Surprisingly, severe neonatal thrombocytopenia (<50x$10^9$/L) is present in only 8-13% of the neonates. Unlike the earlier in this thesis described condition of fetal and neonatal allo-immune thrombocytopenia, severe bleeding complications (i.e. ICH) are very rare in neonates born from mothers with ITP with an incidence of 0-2.9%.[64-72] The nadir of neonatal platelets is mostly seen around postnatal days 3-5; an explanation for this relatively late nadir is not clear yet.[61,69,73-75] Koyama et al reported an increased risk for severe neonatal thrombocytopenia in neonates delivered vaginally, suggesting an additional antibody boost passing the placenta due to uterine contractions. Hypothetically, this could be the reason for the relatively late nadir, but the late nadir for infants born by elective cesarean section can not be declared with this hypothesis. As the nadir of neonatal platelets is postpartum instead of antenatal, risk of intrauterine or peripartum ICH is less prominent. This is confirmed by a total reported rate of intrauterine ICH of 5/23 (22%) of all reported ICHs in neonates from mothers with ITP.[70,76] As peripartum ICH has never been reported, the method of delivery is nowadays only determined by obstetrical indications.[70,72]

Several retrospective studies describe possible predicting factors for severe neonatal thrombocytopenia, only maternal splenectomy and delivery of a previous infant with severe thrombocytopenia were associated with an increased risk for

thrombocytopenia.[65,66,69-72,77,78] Evidence is conflicting, but in most large studies maternal platelet counts (during pregnancy and delivery), maternal antibody state and maternal ITP treatment were not associated with severe neonatal thrombocytopenia.[64,64,66,68,69,71,72,77,79] As antenatal treatment with IVIG seems to prevent ICH in FNAIT without an associated increase in neonatal platelets (chapter 3 in this thesis), this mechanism is perhaps also active in maternal IVIG treatment for ITP. However, this is difficult to prove, because the incidence of ICH is very low in neonates from mothers with ITP during pregnancy.

Considering the extremely small risk of intrauterine or peripartum ICH, one may wonder about the clinical importance of determining risk factors for severe neonatal thrombocytopenia. As the neonatal platelet nadir is on postnatal day 3-5, the greatest bleeding risk is at that moment. Therefore, it makes more sense to focus on optimization of postnatal management, instead of determining possible risk factors. The majority of retrospective studies only appoint the number of infants which receive the different kinds of treatment, without analyzing the effectiveness of each separate treatment, possible due to the small amounts of severely affected infants.[62,65-67,79,80] Only 2 studies described a relatively large cohort of infants recommending one specific treatment: Ballin et al described 11 infants receiving postnatal IVIGs after platelet transfusions and Ovali et al described 6 neonates receiving prednisone after failed postnatal IVIGs. Ballin et al, however, did not analyze the increments after platelet transfusions and IVIG in detail; the effect of prednisone in the study of Ovali et al is dubious as all infants received IVIG prior to prednisone, which is known to take time before becoming effective.[81,82] The study described in this thesis is the first to analyze the course of postnatal platelet values and treatment effects of platelet transfusions and IVIG of each neonate with severe thrombocytopenia individually. We found a substantial relapse rate after multiple platelet transfusions without IVIG, but IVIG did not rule out relapse either. When relapse was occurring during IVIG treatment, this was most likely caused by the fact that IVIG needs a couple of days before becoming effective.

## Recommendation

We recommend checking platelet values from umbilical cord blood, followed by daily platelet counts until postnatal day 5 or until a spontaneous rise (or stable level) is observed. If platelets are $<50 \times 10^9$/L, a cranial ultrasound scan should be made to rule out ICH. Treatment with platelet transfusions is indicated in case of severe thrombocytopenia ($<50 \times 10^9$/L); in case of relapse after the first platelet transfusion

we recommend to add IVIG. When thrombocytopenia persists and does not resolve after treatment with IVIG and multiple platelet transfusions, prednisone therapy can be considered.

### Future perspectives

A randomized controlled trial for optimization of postnatal management of severe neonatal thrombocytopenia due to maternal ITP was never done and would be extremely difficult to perform because of the rarity of the condition. An international prospective registry of all infants with severe neonatal thrombocytopenia due to maternal ITP, containing details about their treatment and platelet course over time, would be very valuable to gain more knowledge for optimization of postnatal therapy. Such prospective registry can be completed with a follow-up assessment on long term, to consider possible effects of antenatal and postnatal IVIG and/or prednisone on long term neurobehavioral outcome.

## Insulin: Short and long term outcome of neonatal hyperglycemia in very preterm infants

Hyperglycemia in preterm infants is caused by a complicated pathway including a combination of insulin resistance and relative insulin deficiency. Due to high circulating levels of inflammatory markers, cytokines and catecholamines resistance to insulin develops, with minimal glucose absorption for storage and no inhibition of gluconeogenesis by the liver. The immature pancreatic β-cells aren't able to compensate for these high glucose levels, as they can almost only produce pro-insulin, which is a 10-fold less active precursor of insulin, leading to relative insulin deficiency.[102-104]
Reported incidence of hyperglycemia in preterm infants is variable, as gestational ages differ between studies and there's still no consensus about a strict cut-off value for a widely used definition of hyperglycemia. In neonates with a birth weight of <1500 grams incidence of hyperglycemia varies between 36 and 68%.[105-108]
Hyperglycemia is associated with increased neonatal mortality.[107-111] ROP, NEC and cerebral white matter damage are also more common in preterm infants with hyperglycemia.[108,109,111-114] A relationship between hyperglycemia and IVH was only established in subgroup-analyses in hyperglycemic preterm infants and in an old study not correcting for confounding factors. Another frequently cited article for the relationship between IVH and hyperglycemia, of Finberg et al, only suggested

a relationship based on the pathophysiological pathway of hyperosmolality leading to intracranial hemorrhage, but didn't describe a population of preterm infants with evidence for this relationship.[110,115-117]

In many centers restriction of glucose intake is the first step in treatment of hyperglycemia. However, adequate caloric intake and weight gain in the first weeks of life are essential for later growth and neurobehavioral development.[118-120] Therefore, restriction of glucose intake must be limited to ensure a minimum intake to avoid malnutrition. Since the early eighties continuous insulin infusion is used to control excessive glucose levels. Advantages of insulin compared to the earlier used glucose restriction policy were less sepsis, higher glucose intake, better growth and more daily weight gain. [121-124]

In pediatric and adult intensive care units tight glucose control seems to reduce morbidity and mortality. This positive effect of tight glucose control in the older intensive care population, led to the hypothesis that this might also be applicable for preterm infants with hyperglycemia.[125-127] Beardsall et al studied an early elective insulin strategy (with prophylactic insulin from the first day of life), leading to a better energy intake, increased lower leg length and less episodes of hyperglycemia. However, mortality at postnatal day 28 and the incidence of hypoglycemic episodes were significantly higher with this early elective insulin policy.[105,128] The use of tight glycemic control, without prophylactic insulin, was also associated with an increased risk for hypoglycemia.[129] Recurrent or prolonged episodes of hypoglycemia are associated with cerebral damage, especially in parietal and occipital white matter and cortex, leading to an impaired neurodevelopmental outcome.[130-132] The advantages of insulin treatment for hyperglycemia need therefore to be balanced against the risks of hypoglycemia.

The only study on long term outcome of hyperglycemia in preterm infants was retrospective and performed by ourselves (outlined in this thesis). We found an impairment of both neurological and behavioral outcome in preterm infants with hyperglycemia, compared to those without. However, all infants received insulin treatment, which obfuscates the possible beneficial effects of insulin for neurobehavioral outcome. Did our infants have an impaired neurobehavioral outcome because of hyperglycemia induced brain damage or was this due to insulin usage with the possibility of undetected episodes of hypoglycemia?[110,133] Unfortunately, above mentioned associations of hyperglycemia with increased mortality and short term morbidity were only reported in study groups who also received insulin.

We concluded that hyperglycemia in preterm infants is associated with neonatal

mortality, short term morbidities and long term impaired neurobehavioral outcome. Despite the ability of insulin to lower serum glucose levels, beneficial effects in reduction of mortality, morbidity and impairment of neurobehavioral outcome have never been shown.

### Recommendation

The real benefits of insulin treatment for hyperglycemia in preterm infants are not clear yet. This is due to the lack of comparisons of mortality, short term morbidity and long term outcomes in infants treated with and without insulin. Until specific advantages or disadvantages are proven, we recommend using insulin to control extreme glucose values. It is pivotal to strictly monitor glucose levels to prevent episodes of hypoglycemia during insulin administration.

### Future perspectives

Comparison of prospectively collected data about mortality, short term morbidities and long term neurobehavioral outcome of preterm infants with hyperglycemia, treated with and without insulin, is necessary to detect the real advantages (or disadvantages) of insulin use. It would be helpful to obtain a uniform glucose cut-off value beyond which hyperglycemia has harmful effects and insulin treatment should be started.

## Main conclusion

The aim of this thesis was to emphasize the clinical importance of retrospective research and the necessity of regular evaluations of currently used treatment protocols. All neonatal pearls described in this thesis were based on practical and clinical questions about currently used protocols; each study contains clinically relevant and usable recommendations for daily medical practice. Despite their retrospective character, which is not the design to gain the strongest evidence, these pearls are very important for neonatal medical health care.

Rare diseases will always be there, health care opportunities will be expanding and populations will continue to change: for these reasons we should continue to reflect on our medical handling and adapt and improve our policies. The chain of neonatal pearls should therefore remain open for new reflecting pearls, so beading can proceed in future.

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