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### Infants at very high risk of cerebral palsy

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# GENERAL DISCUSSION





This thesis started with the description of the intriguing, complex process of early brain development, the multiple factors that may affect it, and questions whether it is possible to positively contribute to this process.

The introduction covered principles of brain development on the basis of the 'modified Kennard principle': *'If you're going to have brain damage, have as little of it as possible. Have it early, and have it on just one side. Be a girl, and come from a supportive family that lives near a good hospital'*. In the following discussion, those principles are presented again, but now discussed in the light of the findings of this thesis, i.e., are the results of the studies in line with the expectations and – last but not least – does this have consequences for early intervention?

### ***'If you're going to have brain damage, ...'***

*'...have as little of it as possible'*

The statement that less severe brain damage results in better outcome than more severe brain damage, was confirmed in this thesis. Both the review (chapter 2) and the intervention studies (chapter 4 and 6) showed that infants with severe brain lesions are more at risk of developing neurodevelopmental disabilities than infants without or with less severe brain lesions. Especially, infants with cystic periventricular leukomalacia (cPVL) with diffuse damage of the white matter, are at very high risk. Percentages of the infants who developed Cerebral Palsy (CP) were 86% in the review, and both in the Vroegtijdig Interventie Project (VIP) and LEARN2MOVE0-2 (L2M0-2) study 100%.

Severity of brain lesion is one of the major predictors for outcome, but not the only factor, nicely illustrated with the findings in the VIP- and L2M0-2-study. Infants in the VIP-study were included on the basis of clinical observation, presenting with definitely abnormal general movements, and only a minority (13% (6/46)) of them had a severe brain lesion. In the L2M0-2 study, inclusion criteria were largely based on severe brain lesions, resulting in 77% (33/43) of the infants presenting with a severe brain lesion. Indeed, better neurodevelopmental outcome was found for infants who participated in the VIP-study than in the L2M0-2-study, in line with the hypothesis 'have as little brain damage as possible'. In the VIP-study, less than a quarter of the infants developed CP, in the L2M0-2-study about half of the infants. However, mentioned numbers also show that severity of brain lesion is not the only predicting factor for outcome: in the VIP-study, the percentage of infants who developed CP was higher (23% (10/44 (2 unknown))) than the percentage of infants with severe brain lesions (13%), i.e., about half of the infants who developed CP did not have a severe brain lesion. In the L2M0-2-study, it was the other way around: most infants had severe brain lesions (77%), but the percentage of infants who developed CP was lower (54% (22/41 (2 unknown))), i.e. part of the infants with a severe brain lesion did not develop CP. The results emphasise that extent and severity of brain lesions are important, but definitely not the only predicting factor for

outcome. Clinical observation, such as use of general movements as shown in the VIP-study, is also an important predictive tool for neurodevelopmental outcome. This is in line with literature findings, which show that combining instruments, such as brain imaging, clinical observation and examination, predict outcome best.<sup>1,2,3</sup>

Concerning possibilities for intervention in relation to severity of brain lesions, the intervention studies showed also interesting findings. In both intervention studies, outcome at RCT-level was comparable for COPCA (COPing with and CAring for infants with special needs) and TIP (Typical Infant Physiotherapy), and no interactions between brain lesion and intervention on outcome were found in the L2M0-2-study. After analysing contents of intervention, specific interventional elements were related to infant outcome in the VIP-study, but not in the L2M0-2-study. These findings may be related to the differences in infant characteristics: as described above, majority of infants in the L2M0-2-study had severe brain lesions and were generally more severely affected than infants in the VIP-study, in which most infants did not have severe brain lesions. Differences in findings may imply that a less severely affected brain may be more susceptible for interventional elements than a more affected brain, which may have less abilities to reorganize and compensate. It raises questions about whether interventions should be specifically tailored to the type and extent of the brain lesion or the infant's clinical presentation. It is conceivable that an infant has to show a certain degree of motor abilities, to be able to intervene on, or to be responsive to motor challenges by the caregiver or physiotherapist. In case motor abilities are very limited due to extended brain damage, challenging is difficult and assistance may be an alternative.

With increasing possibilities of imaging techniques, localizing brain injury becomes more and more accurate, which improves understanding relations between localization, extent of brain damage and outcome.<sup>4,5</sup> It may assist in studying effects of intervention in infants with specific brain lesions. However, literature and this thesis show that clinical observation and examination should not be forgotten.

#### *'...have it early'*

The statement '...have it early' is based on principles of brain plasticity, in which effects of brain damage were measured in a young, immature brain, compared with a more mature brain. In this thesis, predominantly very early brain damage was studied, i.e. in the preterm or term neonatal period. Therefore, I will discuss this statement a little bit different than it is meant by the original principle, and will focus on differences in brain lesions and outcome for infants born preterm in comparison with those born near or around term age.

According to the WHO definition<sup>6</sup>, a preterm infant is born below a gestational age (GA) of 37 weeks, with specification of time frames: moderate to late preterm between 32 and 37 weeks GA; very preterm between 28 and 32 weeks GA; extremely preterm below

28 weeks GA. In the VIP-study, inclusion took place on the Neonatal Intensive Care Unit (NICU), and majority of the included infants was born preterm (91% (42/46)), often very or extremely preterm (78% (36/46)). It reflects a selected NICU-population with a relatively high proportion of preterms.<sup>7</sup> In the L2M0-2-study, numbers are a bit different: 67% (29/43) of the infants was born preterm, 51% (22/43) very or extremely preterm. The differences in GA's, were also represented in type of brain injury: in the VIP-study, infants who had brain lesions most often presented with lesions related to prematurity: periventricular brain lesions or intraventricular haemorrhages. In the L2M-0-2-study type of injury was strongly related to GA: moderately to late preterm and term infants had most often cortical infarctions, basal ganglia or thalamic lesions. Extremely and very preterm infants presented usually with periventricular leukomalacia. Posthaemorrhagic porencephaly was present both in preterm and term infants, but more in preterm infants. What should be noted is, that being born at term, does not mean that timing of brain injury was also near or at term age. For example, posthaemorrhagic porencephaly could be the result of preterm brain injury, but consequences may present after term birth.

It is difficult to compare outcome of the VIP- and L2M0-2-study based on GA's, because more infants with severe brain injury participated in the L2M0-2-study. In the VIP-study, 19% (7/36) of the very to extremely born infants developed CP, in the L2M0-2-study 64% (14/22). However, from the very to extremely preterm infants, only 11% (4/36) in the VIP-study had a severe brain lesion, whereas 82% (18/22) of the infants in the L2M0-2-study had. In both intervention studies, severe brain injury in the form of cPVL, was only present in preterm infants. It resulted in all cases in CP, usually a more severe type. It may reflect the sensitivity of the preterm infant and its brain, in the period in which the subplate is active and in which damage to the subcortical white matter is often diffuse, affecting the important process of neural migration.<sup>8</sup> It may be concluded that the combination of prematurity with severe brain lesions makes infants more vulnerable for severe neurodevelopmental disorders than infants with severe brain lesions at near term or term age. Those findings are comparable with literature.<sup>9,10,11</sup> In this sense, the statement 'have brain damage early' holds not true. But as mentioned before, the original statement does not focus on the period which we investigated now and therefore, we could not extend our findings to later periods of brain development. Another point that should be mentioned is that studies in this thesis and in cited literature have been performed in Western countries, having in general quickly applied and good organized medical neonatal care. Accessibility to standard high care and newly developed interventions for term newborns, such as hypothermia, diminish mortality and morbidity.<sup>12,13</sup> Therefore, concluding that preterm brain injury causes more severe neurodisability than term injury, cannot automatically be extended to countries where access to and timing of providing optimal health care is not as common as in our countries.<sup>14</sup>

Next to the 'best' timing of brain injury, the optimal timing of intervention is an important question. General principles of 'the early the better', based on the principles of brain plasticity, are usually applied, also in our intervention studies. Clear evidence however, that early intervention is better than later or no intervention, is lacking, especially for the very high risk infants.<sup>15,16,17</sup> This thesis does not help answering the question about optimal timing of intervention, because we did not include a control group without or with a later start of intervention, which is in general regarded unethical.

*'...have it just on one side'*

Findings in this thesis endorse the theorem that unilateral brain damage results in general in better outcome than bilateral brain damage. In the VIP-study, the number of infants with severe brain lesions was low (n=6) and lateralization was not specified. In the L2M0-2-study, more than half of the brain lesions were bilateral. Seventy-four percent (14/19) of the infant with bilateral lesions developed CP, all of them bilateral CP. Sixty-two percent (8/13) of the infants with unilateral lesions developed CP, of them 63% (5/8) unilateral and 37% (3/8) bilateral CP. Unilateral lesions resulted more often in less severe CP with lower Gross Motor Function Classification System (GMFCS)-levels,<sup>18</sup> bilateral lesions resulted in higher GMFCS-levels. Results of the L2M0-2-study are comparable with results from the systematic review (chapter 2): unilateral lesions often result in better motor and cognitive outcome than bilateral lesions.

However, it is intriguing that literature and the L2M0-2-study also showed that unilateral brain lesion may result in bilateral CP and vice versa. One of the explanations may be that infants with diagnosed unilateral brain lesions, may also have had some contralateral injury, perhaps too small to identify with used imaging. On the other hand, it may also tell something about the bilateral connections needed for certain motor function, and regenerating or compensating mechanisms within a brain which may compensate for bilateral damage.<sup>19,20</sup> Knowledge and assumptions about underlying working mechanisms of the bilateral working brain, have been implemented in interventions. Examples are the Constraint Induced Movement Therapy (CIMT) and Bimanual Training, specifically targeted at children with a unilateral type of CP.<sup>20</sup> This type of intervention is also under investigation in infancy, with youngest infants of 7 months old, and preliminary results are promising.<sup>21</sup> Prerequisite for starting such an intervention however, is that there should be an asymmetry and generally, at very young age asymmetries are not yet present.

To conclude, I can agree with the statement 'have brain damage just on one side', as unilateral brain lesions result less often in neurodevelopmental disability than bilateral ones. However, as shown in this thesis, individual exceptions are not unusual and may tell us something about the complex wiring of the brain. Interventions targeting asymmetries can just be started when asymmetries become present. Therefore, they seem not to play a

specific role in very early intervention, but studies show promising results after asymmetries have become present, even at young ages.

*'...be a girl'*

Boys are known to be at higher risk of brain lesions and neurodevelopmental disorders.<sup>22,23</sup> The systematic review (chapter 2) showed that sparse information is available on the effects of sex on outcome for infants with severe brain lesions. The studies which did report about sex differences, suggested more boys presenting with brain lesions, but no clear sex differences in motor and cognitive outcome. Findings of the review are in line with findings in the intervention studies. In the VIP- and L2M0-2-study, the number of included boys and girls differed a bit: in the VIP-study participated 20 boys and 26 girls, in the L2M0-2-study 26 boys and 17 girls. Whereas in the L2M0-2-study inclusion was mainly based on brain lesions, the difference may be a representation of the higher vulnerability for brain lesions in boys.<sup>23,24</sup> In both intervention studies, no effect of sex on outcome was found.

The question whether intervention should be sex specific is an interesting one. The first idea that comes to my mind is not to specify when outcome is not known to be different with a clearly known reason. However, you may wonder if intervention already differs for boys and girls, as interaction of caregivers or physiotherapists with boys and girls may differ. This may be related to personal and cultural gender specific views, but also to sex specific infant behaviour.<sup>25</sup>

*'...come from a supportive family'*

As mentioned in the introduction, enrichment of the environment is supposed to have positive effects on infant development. In better socio-economic circumstances, it is usually easier to enrich an environment than in circumstances in which the availability of resources is low. In the systematic review (chapter 2), information about socio-economic status was very limited, and therefore, no conclusions could be drawn from it. In the VIP- and L2M0-2-study, caregivers educational level was used as an indicator for socio-economic status. Socio-economic status is not always related to educational level, and therefore it is only used as a proxy measure. In the VIP-study, regarding cognitive outcome, infants with mothers with lower educational levels seemed to benefit more from the COPCA-intervention than from the TIP-intervention.<sup>26</sup> A hypothesis for this finding may be that one of the core components of COPCA, i.e., challenging infants to discover their abilities, may be more incorporated in daily activities in families with higher educational levels, and less in families with a lower educational level. Therefore, stimulating caregivers to challenge their infant may have more effect in lower educated families, and may enrich the infant's environment and stimulate infants to explore, which may positively influence cognitive development.<sup>27</sup> In the L2M0-2-study however, no effects of educational level on outcome were observed. Again, this



may be related to the studied group: a more injured brain, may be less sensitive for (subtle) intervention effects.

Knowledge about the importance of the family and considering caregivers as the experts concerning their child, resulted in the last decades in development of family centred care principles. Family centred care is based on partnerships between families and professionals, in which information is shared, with mutual and equal respect, and decisions in health care are made within the context of the family, aiming to empower families to make their own decisions in health care.<sup>28,29,30</sup> In chapter 3, developments within regular physiotherapy over the years as applied in the Netherlands were studied, aiming to objectify whether theoretical developments have been implemented in practice. Fitting into developments about family centred care, results showed indeed that family involvement increased over the years. Despite larger family involvement, results also suggested that largest part of involvement was still in a relation in which the therapist informed or showed caregivers how they should perform actions. Therefore the goal to form equal partnerships between professionals and caregivers has not been achieved yet. Results are in line with literature: principles of family centred care are widely accepted, but implementation into clinical practice is not always evident.<sup>29</sup> In COPCA, education to the caregivers was most often provided by means of coaching, indicating more partnership than in the control intervention TIP, where training was more common (chapter 6).

Concerning intervention effects on family outcome, I can only discuss the findings from the L2M0-2- study, as family outcome was not measured in the VIP-study. Interestingly, the only effect of intervention on outcome in the L2M0-2-study was found for family outcome and not for infant outcome: COPCA-related intervention elements were positively associated with family empowerment. With the assumption that intervention may only have limited effects on outcome of very high risk infants, as it may not overrule detrimental effects of brain damage, it is not surprising that in the L2M0-2-study only an association of interventional elements with family outcome was observed. However, if family outcome can be influenced positively, it may be conceivable to have a positive effect on infant outcome at the longer term. More family empowerment may reinforce feeling of control over situations, which may have a positive effect on caregivers well-being.<sup>31,32</sup> If caregivers feel better, it is easier to interact in a positive way with their infant. Positive caregiver-infant interactions may benefit child outcome, for example on child's behaviour or well-being.<sup>33</sup> Apart from a possible positive influence of family empowerment on long term infant outcome, the positive association of interventional elements with family outcome by itself may have attractive consequences for society. Caregivers who are better able to make decisions in the health care process, are more self-managing and less dependent from professionals, which may result in diminishing health care costs. Moreover, if well-being is positively influenced, caregivers utilizing mental health care services may also decrease.

*'...and live near a good hospital'*

Living in the neighbourhood of good hospitals, provides accessibility to the facilities the health care system offers. Whether it is better to live near a good hospital if you have brain damage, sounds logical, but this thesis cannot confirm the statement because all infants had access to neonatal and paediatric care in the Netherlands, which is regarded as high standard care in a Western developed country. Imaging was also available, by ultrasound or MRI. Early accessibility to imaging and high standards of care, makes early detection of infants at high risk possible. However, availability of good imaging techniques does not automatically mean that outcome will be better.<sup>34</sup>

Besides accessibility to good neonatal care, all studied infants had good opportunities for follow-up. All children were monitored by physiotherapists and had also follow-up assessments by paediatricians or child neurologists. Follow-up has several goals: signalling of atypical development, monitoring individual development and predicting future development. Ideally, a measure which has all properties should be used for follow-up. However, practice reveals that it is difficult to develop such a 'gold standard' instrument in infancy.<sup>35</sup> Frequently used measures for children with CP are the GMFCS<sup>18</sup> and the Gross Motor Function Measure (GMFM)<sup>36</sup>, both with good psychometric properties in childhood, but less used below the age of two years. In Chapter 8, use of the GMFCS as a classification measure for the severity of CP in infancy is discussed. It advocates for the incorporation of assisted mobility at early age, as implementation of early powered mobility is more and more common.<sup>37</sup> It is known that motor and cognitive development are interrelated.<sup>38,39</sup> Being able to move and therefore explore the world around, may have positive influences on cognition.<sup>40</sup> Therefore, I not only advocate the implementation of assisted mobility in the GMFCS for classification, but also the use of assisted mobility at young age to broaden the infants world and create the opportunity to explore if motor abilities are not sufficient to do so. Unfortunately, creating such opportunities are in general more available in good health care circumstances than in countries in which health care is less developed. In Chapter 7, use of the GMFM in infancy has been described. The GMFM appeared to be difficult to use in infants. Therefore, some suggestions for adaptations in infancy were made. First results are promising, but should be investigated further. Disadvantage of use of an 'extra' infancy instrument is that later on the 'standard' GMFM-measurement is used, and comparison over time is then more difficult. Therefore, development of an instrument which can be used in infancy and later on, with the ability to detect infants at risk, representing actual functioning and the possibility to predict future outcome, would be desirable. The primary outcome used in the VIP- and the L2M0-2-study, the Infant Motor Profile, seems to have many of suggested properties, but norm data are not yet available. Moreover, it is also an instrument for a specific age range and can only be used until children have had some walking experience. Because infancy is a period in which many changes in development

take place with large variation, it is questionable whether the 'ideal' instrument to measure all properties could be developed. Therefore, the combination of use of instruments, together with clinical examination and use of other information such as imaging, remains important. Combining different sources of information, is most easy in good health care circumstances. However, it should be prevented that it results in 'overclassification'. Purpose of classification and measurement should always be kept in mind and not everything possible has to be done. Deciding about measuring, classification and predicting, should be consistent with interests of families and therefore, could differ per family. Some caregivers want to know exactly what they can expect, some do not. I think that both should be respected, under the condition that it does not harm the infant or the family.

### **Methodological considerations**

Studying infants at high risk for cerebral palsy involves many methodological challenges. The first factor which influences most studies is that – fortunately – prevalence of very high risk infants is low. CP is known to have an incidence of about 2 per 1000 newborns. Not all infants are in the picture from birth onwards as being at risk of CP. In general, families of infants recognized as being high risk have already a large burden of care, and additional participation in research may be too much. Therefore, numbers of infants who are eligible for early intervention studies such as described in this thesis is low.

In the described intervention studies, all infants received intervention, either COPCA or TIP. No control group without intervention was included. Actually, knowledge about development in at risk infants without intervention would be very valuable, as it tells something about the 'natural course'. However, it is hardly possible to realize this, as withholding infants intervention is generally considered as unethical, even if no clear evidence exists that doing something is better than doing nothing. Another option to know more about natural course is to compare developmental outcome with that of infants in countries where early intervention is not as common as it is in the Netherlands. However, besides not receiving intervention, infants usually grow up under other circumstances, and therefore results cannot be compared fairly.

What is striking in many early intervention studies, also in this thesis, that effectiveness is limited. On the one hand, this could be related to the fact that natural developmental course can only be influenced to a limited extent, on the other hand, it can be questioned whether adequate study designs are used. What is known, is that contents of physiotherapy is in general heterogeneous. Physiotherapeutic theories develop over time, and application in practice may be a mix of different ingredients, as a result of individual preferences and experiences.<sup>41,42</sup> Therefore, to compare interventions in a two-arm randomized clinical trial (RCT), may be not the best form, as interventions are heterogeneous and partially overlapping.<sup>43</sup> In the first place, due to the existing heterogeneity, more insight is needed in

what really happens within interventions. Both in the VIP- and the L2M0-2-study, a detailed process analysis was performed, providing insight in real contents of applied interventions. Where no difference in outcome on RCT-level was found, associations between contents of intervention and outcome were present, revealing that it is of added value. Besides the added value, it should be noted that you must remain aware of what has been studied: contents of intervention may be related to infant's, caregivers' or physiotherapist's characteristics. Interrelations between characteristics and outcome may be confounding factors in studying relations between interventional elements and outcome. However, no differences in contents of intervention for infants who did and who did not develop CP were found, which suggests that the influence of confounding is limited. Other alternatives for RCT's which have been proposed in literature are for example practice-based evidence, cohort studies, single subject designs, or qualitative research.<sup>43,44,45</sup>

Another methodological shortcoming in early intervention research is that no 'gold standard' for measuring outcome exists, which makes it more difficult to compare outcome of different studies and for example to use them for meta-analysis. Not only being able to measure infant outcome is important, but also the needs and interests of caregivers.

What is also needed, is more information about dosing of interventions. In both the VIP- and the L2M-studies frequency of interventions sessions was reported, but what really matters is knowing about the transfer of interventional elements into daily life activities. If interventional elements are implemented in daily life, dosing is much higher than in some physiotherapy sessions of 30 to 60 minutes. Unfortunately, data from this thesis are not sufficient to answer the question about what dosage is effective. Therefore, it is recommended to develop adequate and realistic measures for dosing of interventional elements in daily life.

## Clinical implications

Infants at very high risk of developing CP are a challenging population. It is not known whether applying intervention is better than withholding intervention, as we do insufficiently know about the natural course. Results of this thesis and findings from literature<sup>15,16,17</sup> suggest however, that contents of early intervention should be a mix of ingredients and may have to be individually tailored, adapting to characteristics and wishes of the infant and their families. Suggestions for most effective ingredients of early intervention are: challenging the infant, to elicit motor activities, and coaching the caregivers. Both are positively related to outcome, either infant or family outcome. Moreover, results suggest that effects of intervention on infant outcome may differ, depending on the extent of brain injury or clinical disabilities. If the infant is less severely affected, influencing infant outcome may be possible; if an infant is more severely affected, influencing infant outcome may be limited. Our findings may have the following clinical consequences: in less severely affected infants,

challenging motor activities without assistance and encouraging the infant to find his or her own motor strategy, should be encouraged. In more severely affected infants, motor capacities may be too limited for the infant to find a motor strategy on its own, and more assistance may be provided, either by the caregiver or therapist, or by adaptive aids.<sup>17</sup>

The role of the family is important in early intervention, perhaps even more important in higher risk infants than in relatively low risk infants. In general, burden on the family is high, especially if the infant is severely affected, and every developmental phase requires new adaptations. Therefore, not only infants, but also their families are at risk, for example for being overloaded or getting (mental) health problems. Especially in this high risk families, awareness of and taking into account their needs and wants is important. Being aware of these needs and share thoughts about decision making in the health care process, paves the way for family centred care, with partnerships between professionals and caregivers. Caregivers of children with CP indicate that creating partnerships is important, to promote the ability to find the way within the complex care system around them.<sup>46</sup> In the L2M0-2-study, interventional elements like coaching seem to create such partnerships, associated with better family empowerment. Although most professionals agree on the issue of the importance of family centred care, the actual implementation needs more change in current practice. Herewith it is important, that caregivers have still the role of caregivers, who are experts about their child, and that they do not feel being the therapist for their child. Role of professionals should be that they provide caregivers with enough information, with the result that caregivers feel competent and empowered to make their own decisions in the health care process, fitting to the needs and values of the family. It is of importance that caregivers who are less familiar and experienced with self-management, feel also sufficiently supported by professionals. This may mean that professionals coach some families more at a distance and other families sometimes more in a directive way, if this meets the needs of the family.

What has not been mentioned yet, but what is important in my opinion are two other factors, not directly measured in this thesis: 1) intervention should be fun to stay motivated and 2) there should be a good relationship between the physiotherapist and the family. If these conditions are not met, I suppose intervention will not work at the long term. If interventional elements are applied into daily life activities and if caregivers and infants enjoy them, it becomes a habit and not a need. Prerequisite for implementing interventional elements into daily life, is that caregivers have confidence that it is useful to apply. Trust in efficacy requires a good relationship between professional and caregiver. However, assessing the quality of the relationship between professional and caregiver is difficult, as it is not easy to quantify by observation and asking will often give socially desirable answers.

## Future perspectives

This thesis contributes to solving the complex puzzle of effectiveness of early intervention in very high risk infants. Yet, I conclude that still many questions to be answered remain. Future research may help to unravel stepwise the best way to guide infants with special needs and their families.

One of the recommendations to gather more knowledge about developmental courses of high risk infants and efficacy of interventions, is to capture data of high risk infants in large databases and to collaborate nationally and internationally.

Improvement of techniques and measures to detect infants at risk and to predict outcome, may create opportunities to start intervention as early as desired, and to focus on specific characteristics, to be able to provide individually tailored intervention. However, first more knowledge is needed about which interventional elements work for which infants and which timing is best.

Focus until now in infants at risk is often on what factors induce atypical development. However, what is also shown in this thesis is that some infants with poor baseline characteristics, such as severe brain lesions, perform quite well. For future research, it would be interesting to provide more insight in the nature of protecting or favourable factors which result in better outcome, instead of focusing on unfavourable factors. Knowledge about protecting factors may assist in implementing such factors in early intervention.

To provide knowledge about working elements within early intervention, the role of the caregivers is essential. Caregivers are the persons who know eminently what they value and what they miss in interventions and are experts about their infant. Off course, theoretical knowledge and evidence are the basis for developing interventions, but if they do not join caregivers and infant needs, they have a great chance to fail. Therefore, I recommend to ask caregivers who participated in interventions about their opinions and recommendations and to involve caregivers from the beginning in future studies.

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LIST OF PUBLICATIONS

