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Assessment Of Head Asymmetry In Prematurely Born Children During Early Childhood Using 3D Photography

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ASSESSMENT OF HEAD ASYMMETRY IN PREMATURELY BORN CHILDREN DURING EARLY CHILDHOOD USING 3D PHOTOGRAPHY

by

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A THESIS

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ABSTRACT

The aim of this study is to assess the course of plagiocephaly during early childhood in preterm and fullterm children and determine any differences throughout the given timeframe between the two groups. Materials and Methods: 34 preterm and 34 fullterm children born in the Oulu University Hospital, Finland attended the clinical study at the age of 3 (T1), 6 (T2), (T3) months and 3 years (T4). At each visit, 3D images of the head were obtained using a 3dMD head 5-pod camera system (3dMD, Atlanta, GA). Nine outcome variables including 2D and 3D measurements were calculated. Results: At T1, 26.47% of the fullterm and 35.29% of the preterm children had plagiocephaly ($p>.01$). At T2, 17.64% of the fullterm and 21.87% of the preterm infants ($p>.01$), at T3 14.7% of the fullterm and 20% of the preterm children ($p>.01$) and at T4 14.7% of the fullterm versus 16.66% of the preterm children ($p>.01$) had plagiocephaly. Conclusions: Preterm children were more prevalent to deformational plagiocephaly in each timepoint. The prevalence of plagiocephaly decreased through time in both groups. Although the prevalence spontaneously decreases after the first months of life, in many cases does not completely resolve.

Persisting asymmetries may increase the risk of subsequent occlusal and temporomandibular disharmony.

Keywords: Plagiocephaly, Preterm, 3D, Orthodontics

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LIST OF ABBREVIATIONS

2D……...Two dimensional

3D……...Three dimensional

AAP……American Academy of Pediatrics

ACAI……..Anterior Cranial Asymmetry Index

aOR……Adjusted Odds Ratio

AS……...Asymmetry Score

CA……..Corrected Age

CI……...Cephalic Index

CMT……..Congenital Muscular Torticollis

DDH……..Developmental Dysplasia of the Hip

DP……..Deformational Plagiocephaly

EO……..Ear Offset

FS……...Flatness Score

KDE……...Kernel Density Estimate

OCLR……Oblique Cranial Length Ratio

PCAI……..Posterior Cranial Asymmetry Index

PCM……..Plagiocephalometry

RCT……...Randomized Control Trial

ROM……..……Range of Motion

SIDS……..Sudden Infant Death Syndrome

TEA…….....Term Equivalent Age

ULC……...…Unilateral Lambdoid Craniosynostosis

wAS……..….Weighted Asymmetry Score

WHO……..……World Health Organization

CHAPTER 1

INTRODUCTION

Deformational plagiocephaly (DP) is a condition characterized by an asymmetrical head shape which results from external forces applied on the infant's cranium. Common findings in DP are unilateral occipital flattening, anterior displacement of the ipsilateral ear and malar complex, ipsilateral frontal bossing and contralateral occipital bossing[1]. Anterior DP is uncommon.[2]

DP usually occurs during the first months of life and results from supine positioning and preferential positioning of the head.[3] In 1992, the recommendations for infants to sleep in a supine position were introduced by the American Academy of Pediatrics (AAP) so as to prevent sudden infant death syndrome (SIDS). The result of this measure was an increase in the prevalence of DP which was as high as 46.6%.[4, 5] Research shows that the natural course for DP is favorable; occasionally, the deformation persists or even gets worse. In severe cases, surgery is the treatment of choice.[6] Non-surgical treatment is usually effective for patients with DP; active repositioning therapy is the first treatment option followed by helmet therapy if necessary.[7]

The diagnosis of DP is based on the clinical examination but the development of a more accurate measuring system was needed so as to study the natural course of DP and assess the effectiveness of treatment.[8] Recently, 3D photogrammetry has been introduced in the field of craniofacial imaging and has proven to be successful in treatment planning and follow-up cases of DP.[9]

This research project was designed to assess the course of DP in preterm and fullterm children during early childhood using 3D stereophotogrammetry.

Preterm Birth

According to World Health Organization (WHO) preterm birth is the birth that occurs before the 37 weeks of pregnancy are completed. Preterm birth can be categorized in the following subcategories:

1. Extremely preterm: when birth occurs before 28 gestational weeks are completed
2. Very preterm: when birth occurs between 28 and less than 32 gestational weeks and
3. Moderate to late preterm: when birth occurs between 32 and 37 gestational weeks.

Every year, more than 15 million babies are born preterm (more than 1:10) and in 184 countries the prevalence of preterm births ranges from 5-18%. Sixty percent of the total preterm births occur in Africa and South Asia. In low-income countries, about 12% babies are born too early, whereas in higher-income countries this percent is as low as 9%. In 2010, 517,400 babies were born prematurely in the USA.

Preterm birth complications are the leading cause of death among children under 5 years of age. Many of the preterm babies that survive face a lifetime of learning disabilities, visual and hearing problems.

Usually, preterm births happen spontaneously. The most common cause of a preterm birth is the early induction of labour or caesarean birth for medical and non-medical reasons. Other common causes are multiple pregnancies, infections, chronic

conditions (e.g. diabetes, high blood pressure), increased maternal age and genetic influence. Quite often, no cause is identified.

Since the prevalence of preterm births increases worldwide, it is of extreme importance to apply preventive measures. Reducing the complications and the morbidity that is associated with preterm birth starts with a healthy pregnancy. A healthy balanced diet and regular visits (minimum 8) throughout pregnancy are highly recommended by WHO. The importance of quality care before, between and during pregnancy is an essential element in reducing the incidents of preterm births.

More than ¾ of preterm babies could be saved with feasible, cost-effective care that includes essential care during child birth and in the post-natal period, provision of antenatal steroid injections, kangaroo mother care (skin to skin contact for the baby and the mother and frequent breast feeding) and finally antibiotics to treat newborn infections.[10]

Historical Aspects of Deformational Plagiocephaly

According to the literature, the first sign of cranial deformation dates back to 45,000 BC and was found in Iraq[11]. Lekovic et al.[11] in their study reviewed the medical and anthropological literature as well as the anthropological collections of the Arizona State University and the San Diego Museum of Man. Their study showed that intentional or unintentional cranial deformation was practiced by civilizations as old as the Olmec and Maya (1200 BC and 2000 BC respectively). Nowadays, intentional cranial deformation is not being practiced by modern civilizations with the exception of some societies in Africa and South America.[12] Even though DP has been described and recognized as a medical condition since prehistoric times, the first time that its treatment was discussed was in the late 1950's at the Johns Hopkins Hospital.[11] In 1962,

P. M. Danby[13] published the first prospective study on DP. A few years later, the first studies suggesting helmet therapy as a treatment option for DP were published.[14, 15]

Cranial Development and Growth

The 7th week of gestation marks the initiation of cartilage formation in the embryonic skull. During the 8th week, ossification centers in the calvaria and the frontal bone appear and during the 9th week, ossification centers can be found in the parietal, upper and lower squamous parts of the occipital bone. Completion of ossification occurs after birth[17].

Sutures and fontanelles separate the bones of the skull at birth, enabling the passage of the head through the birth canal. Postnatally, these structures are of extreme importance since they are not only growth sites but they also allow the baby's skull to adjust to the continuous brain growth during the first years of life.[16]

As stated in Moss's functional matrix theory, cranial growth is a combination of both capsular and periosteal matrices. Growth of the neurocranium is achieved by both spatial translation and changes in form.[17] The development of the brain leads to an increase of the head circumference; from the midgestational period to the time of birth, head circumference almost doubles. After birth, head circumference continues to increase rapidly and around 6 months of age, the growth rate decreases.[18] From then on, head growth is still present but occurs in a much slower pace until adulthood. The continuous growth of the neurocranium over a long period of time is what makes it susceptible to environmental forces that can potentially alter its shape.[19]

Clinical Characteristics of Deformational Plagiocephaly

DP describes an asymmetrical head shape that results from asymmetrically applied external forces on the infant's cranium. Infants with DP have different clinical characteristics which depend on the severity of the deformation. Mild DP consists only of unilateral occipital flattening; typically, DP is characterized by a parallelogram head, with anterior displacement of the ear and frontal bossing in the affected side and occipital bossing on the non-affected side. In more severe cases, facial and mandibular asymmetry is likely to be observed. Rarely, some infants experience a situation termed "occipital lift" which describes a superior or lateral bulging and is considered to result from the decompression of the brain either vertically or temporally.[1, 20]

Another result of the occipital flattening is the skull being shortened; consequently, the skull of the affected infants has a wider appearance. In cases where the occipital flattening is more extended and the head has a more symmetrical appearance, the condition is deformational brachycephaly.[1, 21] Additional clinical characteristics of DP are a bald spot on the flattened area along with irritated skin, resulting from the prolonged external forces. Restricted cervical range of motion (ROM), a preferred head position, asymmetrical or delayed motor development and abnormal muscle tone are also findings in infants with DP; there is evidence though that the aforementioned are most likely the cause and not the result of DP.[22-25]

Clinical Feature	**Prevalence**
Unilateral occipital flattening	100%
Ipsilateral frontal bossing	89%
Contralateral occipital bossing	95%
Vertex view parallelogram shape	89%
Posterior view normal	99%
Ipsilateral anterior ear shift	93%
Facial asymmetry	8%
No skull deformation at birth	92%

Ultrasound: patent sutures	100%
Signs of sutural fusion in x-ray (if taken)	0%
Signs of sutural fusion in MRI (if taken)	0%

Table 1. Prevalence of different clinical features in a sample of 261 infants with DP, aged =<12 months. Adapted from Linz et al.[26].

Figure 1. Typical demonstration of DP from the vertex point of view.

Epidemiology of DP

In 1992, the prevalence of plagiocephaly was 1in 300 live births. 5 years after the implementation of the "Back-to-Sleep" campaign from the American Academy of Pediatrics (AAP) the rates of plagiocephaly were increased to 1 in 60 live births.[27, 28] Hutchison et al.[29]in their longitudinal cohort study examined 200 infants in Australia in 5 timepoints: 6 weeks, 4 months, 8 months, 12 months and 2 years. Their results showed that the point of highest prevalence was at the age of 4 months (19.7%) and decreases as infants grow older. At 2 years of age, only 3.3% of the infants had plagiocephaly.

Van Vlimmeren at al.[30]designed a prospective cohort study, including 380 healthy Dutch neonates. In this study, the prevalence of DP increased from 6.3% at birth to 22.1% at 7 weeks of age. Peitsch et al.[31]in their cross-sectional study of 201 newborns reported 13% prevalence of "localized cranial flattening" in singletons and 56% in twins. Mawji et al.[5] published their prospective cohort study in which 440 healthy, fullterm Canadian infants were assessed for positional plagiocephaly at the ages of 7 and 12 weeks. Their results show that the prevalence of positional plagiocephaly can be as high as 46.6%. In another cross-sectional study published by Roby et al.[32], 1,045 children aged 12 to 17 years were assessed for positional plagiocephaly and brachycephaly and the results show that only 2% of them were affected.

The prevalence of DP in preterm infants has not been studied extensively; recently, a study group from Germany designed a cross-sectional study including 195 German infants. The results of their study showed 38% prevalence of DP in very preterm and 18% in late preterm infants at term equivalent age (TEA), whereas in fullterm infants prevalence of plagiocephaly was 15%.[33] Another study published by the same study group, assessed for DP 56 infants born before 32 gestational weeks. In this case, prevalence was 34% at discharge, 46% at 3 months corrected age and 27% at 6 months corrected age.[34] Another prospective study included 120 infants born prior to 30 gestational weeks and showed that prevalence of DP at TEA was 30%, 50% at 3 months CA and 23.3% at 6 months CA.[35]

The previous studies demonstrate that the prevalence of DP increases from birth with the point of highest prevalence being around 3 months of age; after that, prevalence of DP decreases.

Etiology of DP

The etiology of DP lies on the fetus' or infant's environment.[36] During pregnancy and the first years of life, the skull is malleable and vulnerable to external forces. In case where environmental forces are applied asymmetrically on the cranium for a long period of time, cranial growth will deviate from the normal, resulting in DP[37].

Pre- and Perinatal Deformation

Early studies demonstrated that DP is associated with pre- or perinatal problems. In these studies, infants with congenital muscular torticollis (CMT) usually had DP as well; these two conditions were considered to result from limited intrauterine space.[13, 14, 38] Even though a cross-sectional study that was released on 2008 showed that the majority of newborns have some kind of cranial asymmetry,[39] a year earlier, van Vlimmeren et al.[30]in their study showed that DP at birth was not predisposing for DP at the age of 7 weeks. In other terms, they showed that DP at birth is a temporary condition. Most of the factors that increase the risk of DP at birth do not increase the risk for DP in later infancy. In the majority of cases parents first notice the deformation only a few weeks after birth.[30, 31] Nowadays, we believe that most children with DP develop the condition after birth. In cases where there is even mild prenatal flattening that could act as a factor for developing DP in the future, even though there is not enough evidence to support such a finding.[19, 40, 41]

Postnatal Deformation

Gaining control of the head position is a process that is completed within a few months. Until then, the infant will remain in the position placed in. Staying at the same position for a prolonged period of time results at a force being applied asymmetrically from the contacting surface to the infant's cranium. That asymmetrical

application of force may affect the growth of the cranium resulting in DP if the infant tends to keep the head turned to the same side.[19, 21]

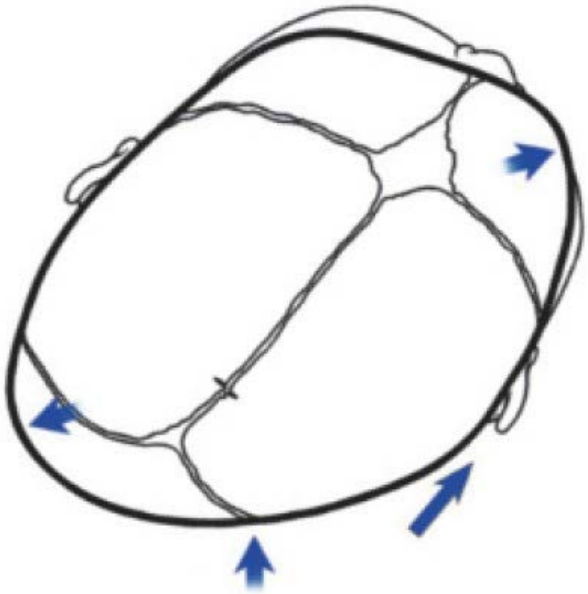

Figure 2. Asymmetrically applied external forces on the cranium may alter the cranial growth resulting in DP.

The deformation of the cranium usually occurs between birth and when the infant becomes capable of crawling and sitting. After that period, supine positioning of the infant is minimized and therefore the environmental forces applied on the infant's cranium are significantly reduced. The time at risk varies greatly between infants and it has been shown that infants born prematurely as well as those with slow motor development are more likely to develop DP.[41] The supine sleeping position has been proven to inhibit some aspects of infant motor development such as rolling prone to supine, tripod sitting, creeping, crawling and pulling to stand attained later resulting in DP. All of the above explain the increase in the prevalence of DP after the supine sleeping position was introduced by the AAP.[39, 40]

Risk Factors for Deformational Plagiocephaly

There are many factors associated with increased risk for DP. Limited neck ROM, infant positional preference or parents not altering the infant's head position regularly are considered to be major risk factors for DP in infancy.[29, 30, 42, 43] Some other factors increase the prevalence of DP through increasing the risk for positional asymmetry and/or slower motor development.[30, 40, 43-45] So far, several studies have examined the effect of different factors on the risk of DP at or before 4 months of age; yet the effect of environmental factors on the prevalence and the course of DP has not been studied. Table 2, summarizes risk factors reported in case-control and cohort studies.

Risk Factor	Reference (author, year)			
	Hutchinson et al. 2003[47] aOR (95% CI)	Hutchinson et al. 2004[31] aOR (95% CI)	Van Vlimmeren et al. 2007[32] aOR (95% CI)	McKinney et al. 2009[50] aOR (95% CI)
Male sex	2.5 (1.2-5.2)	NS	5.4 (1.9-15.3) at 0W 2.0 (1.1-3.4) at 7W	2.0 (1.8–2.2)
Primiparity	2.9 (1.5-6.0)	NS	2.4 (1.4-4.2) at 7W	2.2 (2.0–2.5)
Assisted delivery	NS	NS	NS	1.4 (1.1–1.8)
Prematurity	3.3 (1.0-10.5)	NS	-	1.7 (1.5-1.9)
Twin	NS	NS	-	3.2 (2.7-3.7)
Small for gestational age	-	-	-	1.6 (1.3-1.9)
Birth trauma	-	-	-	1.4 (1.2-1.7)
Congenital anomaly	-	-	-	2.0 (1.8-2.3)

Torticollis (any)	-	-	-	57.7 (16.5-202.1)
Limited passive neck rotation at birth	20.4 (5.8-71.4)	9.5 (2.6-34.9) at 6W 6.5 (1.9-22.3) at 4M	NS	-
Risk Factors	Reference (author, year)			
	Hutchinson et al. 2003[47] aOR (95% CI)	Hutchinson et al. 2004[31] aOR (95% CI)	Van Vlimmeren et al. 2007[32] aOR (95% CI)	McKinney et al. 2009[50] aOR (95% CI)
Limited active rotation at 4 months of age	NS	3.1 (1.2-8.1) at 4M	-	-
Early established positional preference	37.5 (8.4-166.3)	-	9.5 (5.3-17.0) at 7W	-
Always sleeps head turned to same side	7.1 (2.8-18.4)	4.3 (1.6-11.6) at 4M	7.5 (3.9-14.4) at 7 W	-
Infant only bottle-fed on same arm	-	-	1.9 (1.0-2.6) at 7W	-
<1 hour upright	-	4.0 (1.4-11.2) at 6 W	-	-
Placed prone <3 times/day	2.3 (1.0-5.0)	NS	2.4 (1.1-6.2) at 7 W	-
Supine sleeping	7.0 (3.0-16.5)	5.3 (1.8-15.4) at 6W	NS	-
Inactive infant	3.2 (1.4-7.6)	3.3 (1.2-9.3) at 4M	-	-
Motor development ahead of average	-	-	0.6 (0.4-0.9) at 7W	-
Infant temperament average to difficult	-	3.3 (1.2-9.3) at 4M	-	-
Maternal educational level				
Low	5.6 (2.0-15.6)	NS	NS	NS
High	NS	NS	NS	1.2 (1.1-1.4)

0W=birth; 6W=6 weeks of age; 7W=7 weeks of age; 4M=four months of age; NS=factor not statistically significant; dash (-)= factor not assessed in the study

Table 2. Risk factors for deformational plagiocephaly in infancy and their respective adjusted Odds Ratio (aOR) from previous publications. If risk for deformational plagiocephaly at a particular age was investigated, it is reported after the respective aOR. Adapted from H. Aarnivala.

The Role of Cranial Sutures

Before DP was studied in depth, DP and unilateral lambdoid craniosynostosis (ULC) were considered to describe the same condition. The difference between the two was that true DP self-improves, whereas a deformity that persists or deteriorates over time is determinant of ULC; in that case, conventional treatment is not effective.[46] Later on, several studies showed that DP and ULC are two entirely different conditions, with very specific clinical and radiographic features.[20, 47-50]

Differential Diagnosis of DP and ULC

A distorted cranial shape results either from an external deformation or from craniosynostosis; clinical examination can reveal the cause of the deformation.[48] The two entities have particular clinical findings that enable us to differentiate one from the other. In ULC, from the vertex point of view, the shape of the skull is typically trapezoidal and the ear on the affected side is displaced posteriorly. On the other hand, from the same point of view, in DP the cranial shape is parallelogram whereas the ear on the affected side is displaced anteriorly. From the posterior point of view, in ULC the shape of the head is a parallelogram and there is an inferior cant to the ipsilateral skull base. Looking from the same point of view, in DP the cranium appears to have a fairly normal shape.[26, 50] Furthermore, in ULC there is usually a thick palpable ridge over the fused cranial suture whereas in DP there are no palpable ridges and the anterior fontanelle is open and soft.[2] Finally, in cases of craniosynostosis the asymmetry is usually present at birth whereas in DP the asymmetry develops during the first months of life.[26]

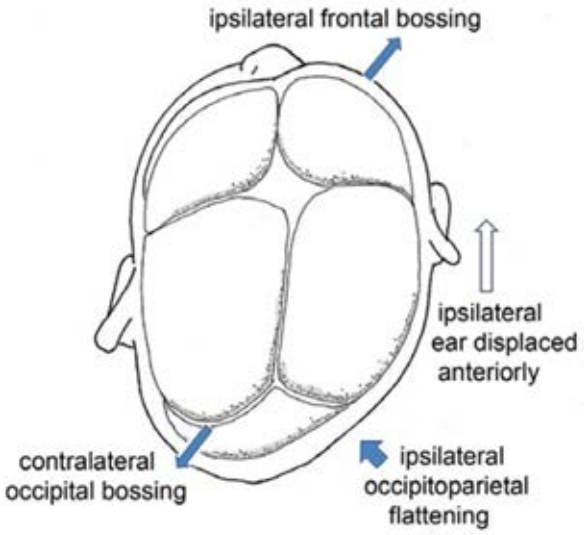

Figure 3. Typical appearance of the cranium in a case of DP from the vertex point of view.

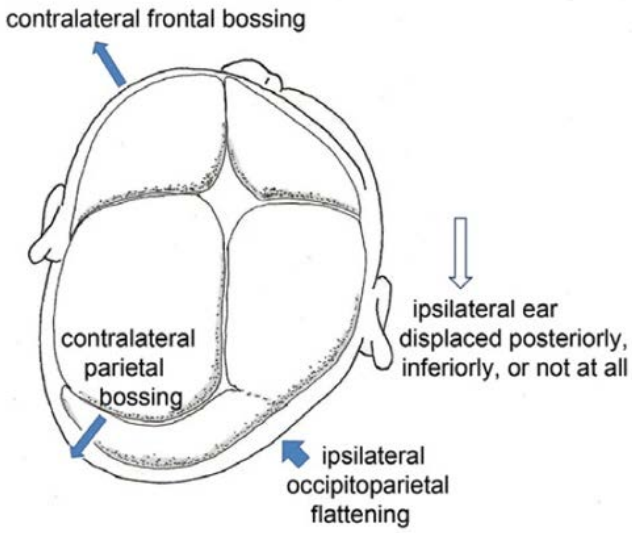

Figure 4. Typical appearance of the cranium in a case of ULC from the vertex point of view.

Radiographic Findings of DP and ULC

In cases of severe deformation accompanied with clinical findings that are indicative of synostosis, the use of radiographic imaging is necessary so as to reveal if the sutures are fused or not.[51] Even though differential diagnosis by physical examination among ULC and DP is possible for an experienced doctor, inexperienced examiners may find it hard to differentiate the two conditions even with the use of conventional cranium x-rays. Studies that used CT scans to compare patients with DP to patients with ULC have revealed differences in the endocranial morphology between the two groups, showing a statistically significant difference in the angle of deviation from the midlines of the anterior and posterior cranial fossae. In patients with ULC there was a significant deviation of the midline from the endocranial fossa whereas in patients with DP the deviation was minimal.[52] Apart from the differences in the endocranial morphology, there were also differences in the temporomandibular joint. In patients with ULC, the temporomandibular joint was significantly displaced posteriorly in the contralateral side, whereas in patients with DP the temporomandibular joint in the majority of cases was symmetrical. Interestingly, the size of the mandible was not significantly different in the two groups.[53] Ectocranial ridging is characteristic of craniosynostosis and absent in patients with DP. In DP, lambdoid sutures have demonstrated areas of focal fusion, endocranial ridging, narrowing, sclerosis and changes from overlapping to end-to-end orientation.[49] Collett et al.[54]in their study used MRI and showed that in patients with DP brain volume is unaffected but brain shape is altered and coincides with the pattern of the deformation. CT scans have been used in many craniofacial centers as primary diagnostic tools. The increased sensitivity and specificity of the images come at the cost of the high dosage of radiation.[52, 55] Even though the accuracy of MRI has not been studied in depth, there are a lot of researchers

who consider it as accurate as the CT scan. MRI's disadvantage when compared to the CT scan is that sedation of the infant is necessary.[26] Sze et al. were the first to prove the reliability of ultrasonography. Their study showed that the sensitivity and specificity of sonography is 100% and 89% respectively in determining a patent from a fused suture.[56] A few years later high frequency sonography was used to examine sutures in 100 infants with skull deformation; the researchers were able to determine the open sutures in 99 out of the 100 infants.[51] In the most recent study about the use of ultrasonography in the diagnosis of DP, Linz et al. concluded that sonography was effective in determining the open sutures in patients with DP and the fused lambdoid suture in subjects with ULC. They also recommend the use of sonography as the primary screening tool for suture fusion in order to avoid radiation exposure and sedation of the infant. If an extra tool is necessary for the confirmation of the findings, plain radiographs are suggested.[26]

Genetics

Craniosynostosis can be either an isolated finding or occur as part of a syndrome. Alterations in the gene family coding for FGFR-1, -2 and -3 have been shown to be related with the fusion of a suture in most craniofacial syndromes including Crouzon's, Apert's and Pfeiffer's.[57] Additionally, in some craniofacial syndromes premature fusion of a suture is related to abnormal function of the transcription factors TWIST and MSX2.[17] A recently published study identified mutations in 14 different genes resulting in a total of 57 genes associated with craniosynostosis.[58] In cases where synostosis is part of a syndrome, usually more than one sutures are fused prematurely in addition to the typical clinical findings associated to the particular syndrome.[17] In syndromic patients with craniosynostosis, genetic testing can play an important role in identifying the exact etiology of craniosynostosis providing crucial information for the

treatment of choice. However, according to the literature, neither ULC nor DP has a genetic basis, even though DP is usually present in syndromes.[24, 59-61] Therefore, differential diagnosis between DP and ULC cannot be done with genetic testing.

Diagnosis of DP: Quantification of cranial asymmetry

In order to understand the natural course of DP and to assess the outcome of treatment, it is necessary to establish a reliable standardized method to measure the positional cranial asymmetry. Even though there are several ways of measuring the cranial asymmetry (from visual assessment to digital photography and ultrasonography) the method of choice nowadays is 3D imaging.[1, 23, 62, 63]

Visual quantification

In clinical practice, the initial need for evaluating the infant's cranial shape derives from either the parental or expert's concern and is related to esthetics. The Argenta classification system is being used to classify DP in five different categories according to the presence of specific clinical findings that are particular for DP. Some of these findings include occipital and frontal asymmetry, ear deviation, occipital lift and facial asymmetry. The Argenta classification system facilitates diagnosis as well as the clinical course of DP.[1]

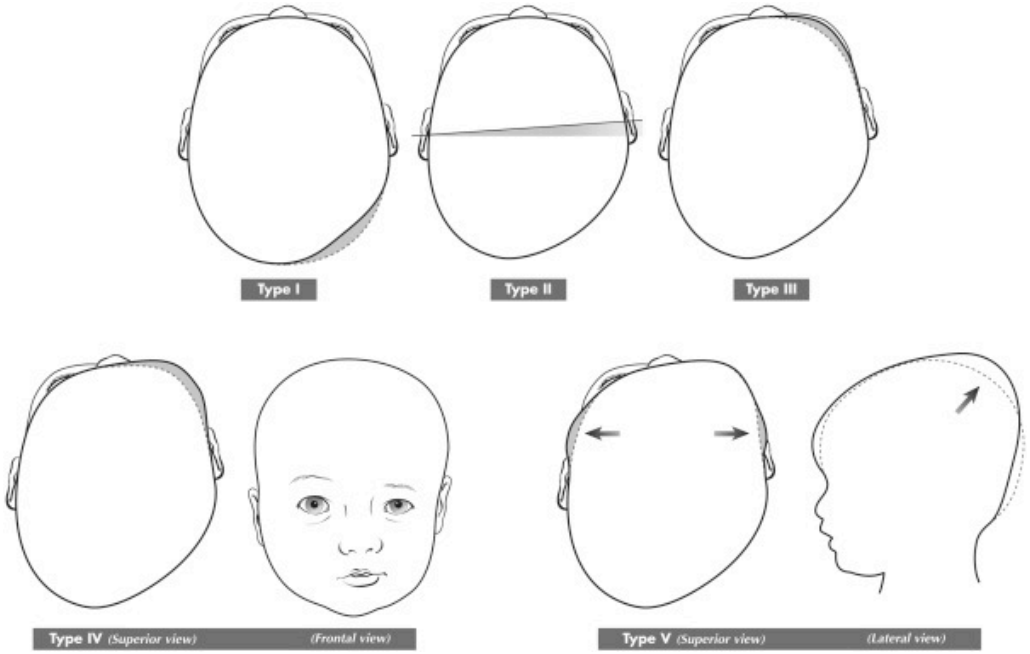

Figure 5. Argenta classification system. In Type I there is only occipital asymmetry, in Type II displacement of the ear is added, in Type III deformation of the forehead is added, in Type IV deformation of the malar is added and in Type V either occipital lift or temporal bulging is added. Originally published in: A Collection of Images and Illustrations by the Department of Plastic Surgery, Wake forest University of Medicine. Used with permission.

The Argenta classification system has been very popular among practitioners not only for the classification of DP but also for determining the length of treatment and recovery time.[64, 65] However, a study published by Spermon et al.[66] shows that the classification according to Argenta is only a moderately reliable method for classifying DP in clinical practice.

Two –Dimensional techniques

Since historical times, the use of anthropometric measurements has been very common in measuring and quantifying severity and changes in DP. Calipers have been used in measuring transcranial diagonals with the difference between the two diagonals

(either reported in millimeters or as an asymmetry index) being indicative of the severity of DP.[8]

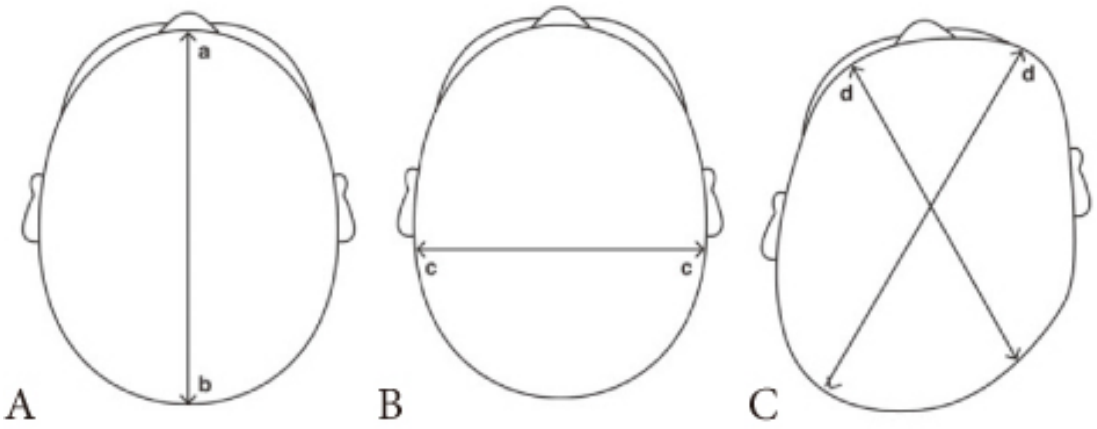

Figure 6. Anthropometric measurements. (A) Cranial length. (B) Cranial width. (C) Transcranial diagonals. a, glabella; b, opisthocranion; c, euryon; d, frontotemporale

Two of the most popular indices are the oblique cranial length ratio (OCLR) and cranial vault asymmetry index (CVAI). In fact, the two indices are very similar: OCLR is the ratio between the longer and shorter transcranial diagonals multiplied by 100%, whereas the CVAI is the difference between the longer and shorter transcranial diagonals divided by the shorter diagonal multiplied by 100%.[23, 66, 67] Different practitioners use different ways of measuring the transcranial diagonals: some use a fixed angle to the anteroposterior midline whereas others use specific craniofacial landmarks or just measure the diagonals at the site of the greatest deformity.[36, 68-70] In a study published in 2007, Glasgow et al.[71]showed that the caliper measurements and the visual assessment of asymmetry correlate very well.

Measurements using calipers are called direct measurements. Their major disadvantages are the difficulty of identifying the craniofacial landmarks and standardizing the infant's head position every time a measurement is taken. Another

disadvantage of the direct measurements is their inter-rater reliability which varies from moderate to excellent.[8, 72] However, standardized measurements are highly reproducible to quantify early childhood head deformity. Repeatability of these measurements is essential to define diagnosis and the severity of the case, as well as the desired treatment modality.[73]

The repeatability of caliper measurements has been questioned and so indirect measurement methods have been developed. In a study published in 2001, Loveday and de Chalain used an artist's flexicurve to acquire a circumferential head tracing, traced it on paper and measured the transcranial diagonals.[74] This method, has been shown to have excellent intra- and inter-rater reliability.[75]

A similar technique was developed and described by van Vlimmeren et al. They positioned a strip of thermoplastic material around the infant's head at the level of the maximum transverse head circumference. Shortly after placement the strip is cured and hardened and three landmarks (the two ears and the nose) are identified. Upon removal of the ring, the middle of the posterior distance between the two ears is also identified. Then, the upper side of the ring is copied onto paper and onto transparent sheet and nine lines are drawn. Using these lines we can obtain indices measuring the ear deviation, flattening of the skull and the cranial proportions. This method is called plagiocephalometry (PCM).[76] The intra- and inter-rater reliability of the PCM has proven to be excellent and the measurements obtained from PCM are very close (1mm difference) to the measurements obtained by CT scans.[76, 77]

The development of digital photography led to the development of new techniques for the quantification of head asymmetry. A method called HeadsUp was developed by Huthinson et al.[78] on 2005. With this technique, a standardized digital photograph is being automatically analyzed by computer software. The transcranial

diagonals, ear deviation angles, OCLR and cranial index (CI) (CI is used to describe brachycephaly and is the ratio between the maximum cranial width and maximum cranial length) can be accurately obtained. When compared to the flexicurve method, the HeadsUp technique seemed to have better repeatability and improved compliance as well as acceptance from the mothers.

Zoneshayn et al.[79] also suggested a technique using a headband whereas Schaaf et al.[80]developed their own method using a digital photograph without a band.

Three-dimensional techniques

The development of 3D imaging led to the implementation of this technology in the diagnosis and quantification of cranial asymmetry. One of the advantages of 3D imaging techniques is that they enable capturing of the entire cranium which allows obtaining not only point-to-point measurements but more importantly measurements of angles, surfaces and volumes.[9]

Digital stereophotogrammetry is the most common method for acquiring 3D images. In this case, multiple synchronized cameras, positioned in different angles, capture simultaneously a picture of the head. The different pictures are being processed by a computer software program and the final result is a 3D image of the head. Capture time is about 1.5 milliseconds, not allowing for any artifacts on the image due to infant movement. However, in order for a proper 3D image of the head to be acquired, it is necessary for the infant to be able to support their head in an upright position. That means that this technique is unsuitable for newborns.[81] Another method used to produce 3D images of the head in infants, is based on laser scanning. In this case, exposure time is about 3 seconds and the scanner is crib-shaped. As a result, the laser scanning method

has very limited clinical use. However, both techniques produce essentially similar 3D images.[82]

Measurements can be taken from the 3D images either manually or by using a specifically designed computer software program. In the latter case, before extracting any measurements it is necessary to standardize the image position and define the planes of interest. In order to do that, specific landmarks need to be identified first and then the software is used to align the picture.[86]

The symmetry related measurements used in the literature include not only the transcranial diagonals but also variables that describe the distribution of normal vectors on cranial surfaces and ratios of volumes within different quadrants of the cranium.[83-86] Other measures of symmetry that have been used include a statistical model that calculates an asymmetry score by comparing each point on the cranial surface relative to its contralateral counterpart, as well as a method using the root mean square of the mean difference between each point on the cranial surface within the occipital region.[87-89] Intracranial volume has also been measured from 3D images in infants with craniosynostosis, showing an excellent correlation to the volume measured from a CT scan.[90]

Direct and indirect 2D measurements of transcranial diagonals measured manually have shown poorer repeatability and reliability compared to the same measurements obtained from 3D images.[9] However, another study showed that transcranial diagonals measured with calipers and diagonals measured manually from 3D images have an excellent correlation.[72] Also, measurements obtained from a 3D image compared to manual caliper measurements, tend to overestimate the diagonal lengths and underestimate the OCLR.[9, 72] Transcranial diagonals obtained manually from a 3D image seem to have poorer reproducibility compared to the ones obtained

with a computer software program.[83] In the first case, the craniofacial landmarks have to be visually identified whereas when a software is used, landmark identification process is reproducible which allows the standardization of the image position and the use of a coordinate system to define the points and planes of interest.[91]

Radiographic techniques

Kim et al. and Kwon in their studies compared the ultrasonography method to the caliper method for the assessment of the changes in infants with plagiocephaly but didn't present adequate evidence for the use of ultrasounds instead of calipers.[63, 926] Also, the use of CT scans and MRI is not recommended for the diagnosis of head asymmetry in clinical practice because of the associated risks, unless there is a compelling reason.[77, 93] The use of plain skull x-rays also does not provide any advantage in the quantification of head asymmetry.[94]

Indices used for the diagnosis of DP

The proposed cut-off values for DP are based on the indices using the transcranial diagonals and until recently they were solely based on expert opinion without any information on their sensitivity or specificity. The suggested cut-off values for OCLR according to literature range from 103.5%-106%.[67, 76-78] Wilbrand et al. in their study suggested age- and sex-specific cut-offs for DP ranging from 103.5-104% but there was no reference on how the cut-offs match the visual perception of asymmetry.[67] In another study, Glasgow et al. reported that all infants with diagonal difference (DD; the difference of the transcranial diagonals in millimeters) greater than 0.6 cm had a visually apparent head asymmetry but they did not report a cut-off value or its sensitivity.[71]

Atmosukarto et al. in their study provided a candidate cut-off value for DP but they did not report the sensitivity, specificity or the cut-off value for OCLR. On the other hand, they reported 96% sensitivity and 80% specificity for a cut-off value of 0.035 for their absolute asymmetry score, calculated with a technique based on normal vector distributions represented as fixed-bin 2D histograms.[86]

Vuollo et al. used a smooth kernel density estimate (KDE) of the directional data defined by the normal vectors instead of fixed-bin histograms defined on the spherical co-ordinate plane, achieving better correlation with clinical assessment. They also reported good correlation between the posterior cranial asymmetry index (PCAI; ratio of the volumes of the posterior quadrants of the head) and clinical assessment.[95]

In the most recent study published in 2017 by Aarnivala et al., the most useful measurements as well as their cut-off values for the diagnosis of DP were described. According to their study, OCLR is recommended as the primary measurement for the diagnosis and monitoring of DP with a cut-off value of 104% (83% sensitivity and 97% specificity) for all age groups. They also reported that PCAI and weighted asymmetry score (wAS) can also be used in monitoring head asymmetry. Cut-off value for PCAI is 10.5% (90% sensitivity and 90% specificity) and for wAS is 24.5 (88% sensitivity and 90% specificity).[96]

In our study, the primary measurement for the diagnosis and monitoring of DP is OCLR with a cut-off value of 104%.

Natural Course of DP

The natural course of DP has not been studied extensively; there is only a small number of follow-up studies that provide some information. Hutchinson et al. used the HeadsUp method and OCLR>=106% to define DP. In their study, at the age of 4 months the prevalence for DP was 19.7% and at the age of 2 years was 3.3%. That

decrease in the prevalence of DP was indicative of a spontaneous resolution.[29] Van Vlimmeren et al. in their study used OCLR>=104.0% as the cut-off value for mild DP and OCLR>=108.0% as the cut-off value for moderate DP. They found that of the infants having DP at the age of 7 weeks, 19% still had mild DP and 1% had moderate or severe DP at the age of 5 years (end of the follow-up study). The prevalence of DP at the age of 5.5 years in their study was 4.4%. Regarding the OCLR values, they improved until the age of 24 months and after that remained stable, indicating that spontaneous correction of the asymmetry of the head occurs up to the age of 2 years.[97] The findings of their study are contradictory to the findings of the study of Goh et al. who showed that the improvement potential is directly proportional to the remaining cranial growth.[98]

Roby et al. in their study, obtained measurements from subjects aged between 12 and 17 years of age and reported a prevalence of DP 1.1%.[32] In another study, Feijen et al. using a cut-off value for OCLR>=106.0% to define DP, reported prevalence of 10.3% in a group of randomly selected teenagers.[99]

DP and Developmental Delays

Miller and Clarren and Steinbok et al. conducted retrospective studies about the rate of later developmental delay in school-aged children who were diagnosed with DP as infants. Their results show that 33.0-39.7% of children with a history of DP at infancy comprised a high-risk group for developmental difficulties at school age as opposed to only 7.7-10.5% of unaffected controls.[100, 101] Hutchinson et al. in their study reported that 36% of the plagiocephalic children referred to their clinic were diagnosed with some kind of developmental delay at the time of the referral.[102] A few prospective

studies have found that children with DP are more prevalent compared to normal subjects in motor developmental delays as well as in psychomotor and cognitive developmental delays.[103-105] Children with DP have also been studied on language development. In their study, Korpilahti et al. found that in 51% of 3-year-olds with DP, 21% had severe speech disorders.[106] Collett et al. reported that 3-year-old children diagnosed with DP, receive lower developmental scores compared to unaffected controls. However, this does not mean that DP causes developmental problems but may serve as a marker for developmental risk.[107] In 2011, Hutchinson et al. found that even though children with DP displayed marked increases in delayed development at early infancy, by the time of the final follow-up at the age of 17 months, delays were tending towards expected levels.[108]

As a conclusion, DP serves as a sign rather than a cause for developmental delays.[103, 105, 107] Therefore, it is a general consensus that infants with DP should be examined for developmental delays as early as possible, so as to facilitate not only diagnosis but more importantly preventive measures and treatment modalities.[109]

DP and Association with Facial Asymmetry and Malocclusion

Facial asymmetries are usually present in more severe cases of DP and in some cases persist till later childhood. Hanis et al. in their case-control study, included 112 Finnish children (56 having Developmental Dysplasia of the Hip (DDH), comprising the study group and 56 unaffected subjects, comprising the control group) aged from 5-10 years old. They demonstrated that-compared to the control group-boys and girls of the study group had a chin-point deviation to the right, a more prominent left orbital ridge, a more protrusive nose and upper lip. The facial asymmetry reported

was thought to be secondary to head deformation caused by the immobilization of the affected subjects in the supine position, as none of them had DP when splint therapy was initiated[110, 111]. In a cross-sectional study of 100 children, the authors found that Class II malocclusion, edge-to-edge bite and deviations of the midline were more prevalent in children with history of helmet therapy compared to non-treated controls. However, none of the differences were significant.[112] St. John et al. in their prospective study reported that the mandibular asymmetry in DP is secondary to rotation of the cranial base and anterior displacement of the temporomandibular joint and not the result of primary mandibular deformity.[113]

Parental Concern, Patient Concern and Quality of Life

Usually, parents' concern about the deformed head tends to decrease as the infant's hair grow and they spend less time on parents' lap. In a longitudinal cohort study, 129 infants diagnosed with DP in infancy were re-measured at the ages of 3 and 4 years. It was reported that 35% of them still had mild to moderate and 4% had severe asymmetry of the head. Interestingly, at the time of the follow-up measurements only 13% of the parents were concerned about the head deformity whereas 85% of them were concerned initially.[114] Another study including 65 children diagnosed with DP at infancy and their parents, reported that parents perceived their children's appearance as very abnormal in 2 cases and mildly abnormal in 25 cases; however, only 21% of them were concerned. In the same study it was reported that 7.7% of the children had commented about their head's asymmetry and 4.6% were teased occasionally.[100] Past studies reported no impact on the quality of life of children diagnosed with DP as infants.[99, 100, 115]

Treatment of DP

In infants with DP, parents usually seek treatment because of the possibility of the deformity getting worse and the subsequent effects in child's appearance.[23] The treatment modalities depend on the severity of the deformation at the time of diagnosis and associated neck pathology and include repositioning therapy, physiotherapy and/or helmet therapy and even surgical treatment in cases of severe deformities.[6, 23]

Repositioning Therapy and Physiotherapy

Repositioning therapy can be conducted by either the parents or the caregivers at any given time during the day and consists of active repositioning of the child. The goal is to eliminate the pressure on the affected side of the skull and to reduce the tightness of the neck muscles by encouraging the infant to turn his head to the unaffected side, giving the affected areas the opportunity to remodel.[116] In cases where the infant presents with positional preference, neck muscle imbalance or asymmetrical motor performance, physiotherapy may be the most suitable treatment option. It focuses on the neck muscles trying to promote symmetrical motor development through stretching and strengthening of these muscles.[117] Repositioning therapy with or without physiotherapy is usually the first line of treatment (especially for infants 4-6 months of age) and needs to be attempted before helmet therapy.[23]

However, the data we have about the effectiveness of repositioning therapy and physiotherapy is limited. Van Vlimmeren et al. conducted a randomized control trial (RCT) study on the effect of pediatric physical therapy on positional preference and DP over a 4-month period. They found that in 7-week-old infants with positional preference, during that period, physiotherapy decreased the risk of DP by 46% at 6 months and 54% at 12 months of age.[117] Wilbrand et al. in their RCT found that

stretching exercises and bedding pillows, over a period of 6 weeks, resulted in improvements in positional cranial deformation.[118] In a retrospective series conducted by O'Broin et al., it was reported that repositioning and physiotherapy until the age of 12 months led to a significant improvement in parents' perception of the severity of DP.[119] Hutchinson et al. in their RCT, randomized 126 infants to either positioning treatment or positioning treatment combined with a positioning wrap and followed them up at 3, 6 and 12 months. They reported that both treatment modalities affect the head shape equally.[120] The same group conducted a long-term prospective follow-up study on 129 infants diagnosed with DP before the age of 12 months. The infants were treated with repositioning therapy and by the age of 4 years, 61% had normal OCLR values.[114] Prospective studies comparing helmet therapy to repositioning therapy have, in the majority of cases, showed that repositioning therapy improves the measurements that are related to cranial asymmetry.[7, 74, 89]

So far though, there are no studies comparing repositioning therapy to the natural course of DP.

Helmet Therapy

The first time that a helmet was used to correct a cranial deformation was on 1979 and it was described by Clarren et al.[15] The helmet is designed in a way that restricts growth in the prominent areas of the deformed head and allows growth in the flat areas. Optimum wear time is 23 hours per day; duration of treatment varies between patients and depends on the severity of the asymmetry and on patient's age. Ideally, helmet therapy initiates between 3 and 6 months old.[121] Currently, there are 37 different helmets on the market approved by the Food and Drug Administration (FDA) in the USA.[98] However, older studies about helmet therapy fail to present strong evidence on

the effectiveness of this treatment.[98, 122, 123] Van Wijk et al. conducted a RCT and reported that helmet therapy and cranial deformation following its natural course are equally effective. However, the side effects associated with helmet therapy, led the authors to discourage the use of helmets in cases of moderate to severe skull deformations.[124] In 2016, a studied published by Weissler et al. suggested that in cases with mild to moderate deformities the parents should choose the treatment they prefer whereas in more severe cases, helmet therapy should be the treatment of choice.[23]

Surgical Treatment

It has been shown that DP does not restrict brain growth and does not increase the intracranial pressure.[54, 109] Therefore, surgery is rarely used for the treatment of DP. Marchac et al. in their study compared two different surgical techniques and showed similar long-term morphologic outcomes. However, they concluded that surgical correction of DP is a life-threatening procedure and should be the treatment of choice only in severe cases and only after all other non-surgical therapies have been applied.[6] Even in severe cases of DP, since the condition raises basically esthetic considerations, surgical intervention is questionable.[121]

Age and Response to Treatment

There is evidence in the literature that a successful treatment outcome is closely related to the infant's age; the younger the infant when treatment starts, the more successful the treatment will be. Repositioning and physiotherapy are considered as the treatment of choice until the age of 6 months. At that point, the infant controls his own sleeping position and as a result, the amount of time he spends lying supine is limited.[42, 121] Additionally, helmet therapy seems to be more effective if initiated before the age of 6 months[68, 120] However, their study also revealed a strong correlation between age

at treatment onset and required treatment duration.[125] In a retrospective study by Steinberg et al. the effectiveness of repositioning therapy with or without physical therapy and helmet therapy were compared. Their results suggest that repositioning therapy should be the first treatment option for most cases of positional cranial deformation.[126] After the age of 12 months, helmet therapy is not suggested because the duration of treatment is prolonged and patient's poor compliance leads to an unsuccessful treatment outcome.[127]

Prevention of DP

The understanding of the mechanisms behind DP led to a series of guidelines that aim to prevent DP from occurring. Literature shows that supine positioning increases the risk of DP in two different ways: directly and by delaying certain fine or gross motor developmental milestones.[128] In order to decrease the risk of DP and to enhance the infant's motor development, it is recommended that the infant spends some time on the prone position daily, starting from birth.[129] Spending a lot of time on a daily basis in bouncers, carriers and car safety seats is also not recommended. On the other hand, alternating the supine head position from side to side during sleep and changing the orientation of the infant to outside activity is essential so as to achieve equal distribution of forces on the infant's cranium.[19]

However, most of the data regarding the effectiveness of the measures described above is coming from studies about the risk factors for DP.[30, 43] One prospective control study showed that early postnatal intervention reduces the prevalence of DP but they also reported that the incidence of DP increases because of a lack of stimulation and encouragement of physical movement and not just because of

supine positioning.[130] In a Swedish pilot study it was reported that the early and regular implementation of guidelines given to prevent DP is effective. The small sample size of this study though, does not allow reaching safe conclusions.[131]

The high prevalence of DP and the effort to successfully treat this condition starting from early infancy, shows the importance of preventive measures and the need for further clinical trials in the future.

Null Hypothesis

There is no difference in the prevalence of DP between the preterm and fullterm children during the first three years of life.

Specific Aim of the Study

The specific aim of this study is to determine the prevalence of DP throughout the first three years of life in children born preterm and fullterm. Diagnosis of DP will be done using the 2D measurement OCLR and 3D measurements PCAI and wAS will also be calculated. Finally, in order to assess the head shape, the 2D measurement CI will be calculated in both groups at each timepoint.

CHAPTER 2

MATERIALS AND METHODS

Subjects were recruited from the Clinic for Children and Adolescents, Oulu University Hospital. These subjects attended the study at the age of 3 months (T1), 6 months (T2), 12 months (T3) months and 3 years (T4). Fullterm neonates were born on pre-determined dates between 2012 and 2013 whereas preterm neonates were born in pre-determined dates between 2012 and 2015; all subjects are of Finnish origin. Approval was obtained from the Pohjois-Pohjanmaan sairaanhoitopiirin alueellinen eettinen toimikunta and consent forms were distributed to the parents and properly obtained before data collection.

Subject Inclusion Criteria

- Recruitment within 1-6 days after birth
- Healthy newborns in maternal ward and living in nearby Oulu region
- Preterms at the age of 34-44 gestation weeks in nearby Oulu region

Subject Exclusion Criteria

- Congenital anomalies (craniosynostosis, cleft lip and/or palate)
- Very early discharge
- Parental refusal

Imaging Systems

At each visit, 3D images of the head were obtained using a 3dMD head 5-pod camera system (3dMD, Atlanta, Georgia). The system consists of five modular units of 15 machine vision cameras and an industrial-grade flash system which is synchronized in a single capture. Its ultra-fast capture speed (1.5 milliseconds) makes it ideal for capturing babies/infants who are unable of standing still and thus creating pictures without artifacts. The system allows for a 360-degree full head capture which documents the size and shape of patient's craniofacial complex and cranial geometry. Its accuracy (<0.2 mm RMS or better depending on the mode) provides accurate documentation of the patient's head shape noninvasively throughout treatment. Also, it automatically generates a continuous 3D polygon surface mesh with a single x, y, z coordinate system from all synchronized stereo pairs. The 3dMD software automatically maps all of the color information to the mesh and no stitching is required. All of the above enhance the 3dMD's ability to capture babies/infants in 3D with conditions such a positional plagiocephaly, craniosynostosis and others[110, 132].

Collecting the Data

68 subjects participated in this study; 34 preterm and 34 fullterm children. The 3D images of the head were obtained using the 3dMD 5-pod camera system (3dMD, Atlanta, Georgia) in a standardized manner. First, a tight nylon cap was fitted on the infant's head to avoid hair artifacts. Next the infant was seated on a chair, centered in the 3D scanner, and encouraged to look through a small window in the panel in front

of him, where after five synchronized cameras captured a 360 degree image of the head. Lighting and surroundings remained consistent throughout the study.

Subjects	Preterm	Fullterm
Males / Females	22 / 12	22 / 12
Singletons / Twins	14 / 20	34 / 0
Extremely preterm (<28 weeks)	3	-
Very preterm (28 – 32 weeks)	7	-
Moderate – Late preterm (32 – 37 weeks)	24	-

Table 3. Characteristics of the subjects participating in the study.

Figure 7. The 3D scanner room has enough space for an adult to be holding the infant in position.

Processing of 3D Images

The 3D images were processed and analyzed with Rapidform 2006 (Geomagic, Rock Hill, South Carolina) 3D software system using custom macros written with Visual Basic for Applications (VBA). More complex mathematical

analyses regarding the outcome were performed with Matlab R2014b (MathWorks, Natick, Massachusetts, USA).

The processing steps comprised of the following: (1) First, ready-made software tools were used to remove shoulders and other excess data from the images and to level out possible bumps caused by cap seams. (2) Next, the craniofacial landmarks endocanthion left, endocanthion right, tragion left and tragion right were manually identified on the image. The 3D image position was standardized by using a custom macro that creates a co-ordinate system based on the aforementioned landmarks and the sagittal reference plane (yz) which it constructs with the mirror face method.[86] In the mirror face method, the original facial shell and a mirror shell are registered together using the best fit technique, and the symmetry plane of the resulting structure is treated as the sagittal plane for the original face and head. The reference point of the co-ordinate system was set at the intersection of the sagittal plane and a line connecting the tragions. The transverse reference plane (xz) was defined to run through the point right in the middle of the two endocanthions and origo perpendicular to the sagittal plane, and the coronal reference plane (xy) perpendicular to the other two planes. At this point, the x-, y-, and z-axes have also been defined. (3) After the aligning process, two planes used in measuring the outcome variables were defined. With the transverse plane serving as the base plane, the measurement plane for point-to-point variables (2D variables) was the plane parallel to the base plane at the maximum curvature in the occipital region (i. e. maximum head circumference). The measurement plane for the remaining variables (3D variables) was defined as running parallel to the base plane, immediately above the highest part of the helix of the higher ear set.

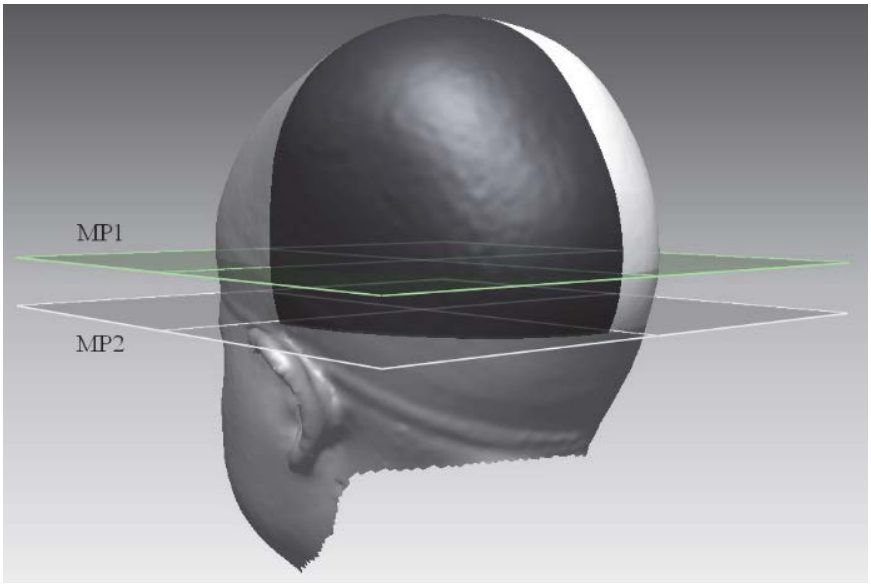

Figure 8. For 2D (point-to-point) variables, the measurement plane (MP1) was the plane parallel to the base plane at the level of maximum posterior curvature in the occipital region (maximum head circumference). For 3D variables, the measurement plane (MP2) was also parallel to the base plane, immediately above the highest part of the helix of the higher set ear. Different colors express the division of the cranial surface and volume into quadrants by the sagittal plane, coronal plane and MP2.

Parameters Measured

From the standard digital photographs, the variables oblique cranial length ratio (OCLR) and cephalic index (CI) were measured using custom-written computer software. From the 3D images, the 2D variables OCLR, diagonal difference (DD), ear offset (EO), and CI were calculated as indicated in Fig. 8. The 3D volumetric variables anterior cranial asymmetry index (ACAI) and posterior cranial asymmetry index (PCAI) were calculated from volumes within the quadrants shown in Fig. 7 using the formula: (larger cuboid volume – smaller cuboid volume) / smaller cuboid volume x 100%. Finally, three 3D surface variables based on normal vector distribution were calculated: asymmetry score (AS), weighted asymmetry score (wAS), and flatness score (FS). AS, wAS, and FS scores are calculated from the surface area within the posterior quadrants by integrating the KDE function. The square of KDE function is integrand in FS, while the square of difference between the KDE function and its

reflection against the sagittal plane is integrand in AS. In wAS, AS is multiplied by a weight coefficient, which is the distance of the outermost point of the occiput from the sagittal plane divided by maximum cranial width. The KDE of spherical data was used.[136] The transcranial diagonals for OCLR and DD were measured at a 40° angle to the anteroposterior midline from the 3D images. The primary measurement used for diagnosing DP was OCLR, with the cut-off value being >=104.0% as described by Aarnivala et al. PCAI and wAS were also used during the study, with their cut-off values being 10.5% and 24.5 respectively, as they have been proven to be useful in monitoring cranial asymmetry.[101] The severity of plagiocephaly at each timepoint was described as mild when OCLR ranges between 104.0-108.0%, moderate when OCLR is between 108.0-112.0% and severe when OCLR>=112.0% as described by van Wijk et al.[129]

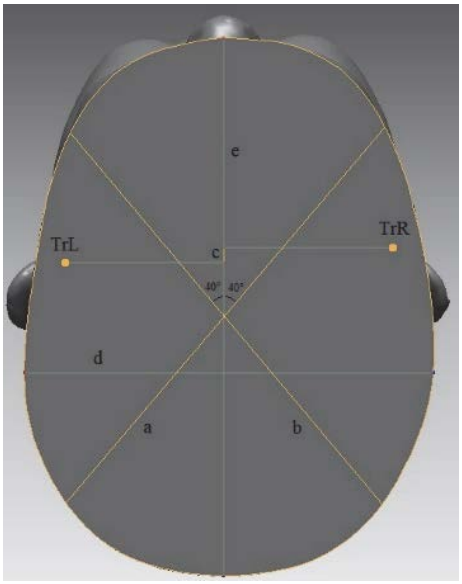

Figure 9. OCLR=ratio of the longer and shorter oblique transcranial diagonals (a,b) x 100%. DD=difference between the transcranial diagonals. Ear offset=distance between the tragion landmarks (TrL, TrR) in the anteroposterior direction (c). CI=maximum cranial width (d) divided by maximum cranial length (e) x 100%.

Statistical Analysis

The distribution of each continuous variable was described using mean and standard deviation for normally distributed values and using median and interquartile range for nonnormally distributed values. Frequencies of categorical variables were also presented. Bivariate comparisons of demographic and cranial symmetry characteristics by term/preterm status were conducted using the chi squared test or Fisher's exact test for categorical variables and using the test or the Wilcoxon rank-sum test for continuous variables. Linear mixed models evaluating the relationship between cranial symmetry outcome measures and term/preterm status over four timepoints were also constructed, to account for repeated measures. Each timepoint was treated as a class variable. Interactions between term/preterm status and timepoint were tested and significant interaction terms were included in final models for each outcome. The LMM for OCLR was also adjusted for dolichocephaly, which was defined as a CI >76. Cranial measurements OCLR, CI, wAS and PCAI were treated as continuous outcomes and DP was a binary outcome (logit model). Term-preterm group differences at each timepoint were tested using the chi squared test. All analyses were conducted using SAS Version 9.4 (SAS Institute, Inc., Cary, NC)

CHAPTER 3

RESULTS

Sample Size

The sample size included two groups with a total of 68 subjects each (34 preterm and 34 fullterm children). Table 4, shows the anthropometric measurements acquired at each timepoint for both groups; mean values, standard deviation (SD) and p values are reported. Table 5 shows the mean values, SD's, term-preterm differences and p values for the 2D measurement OCLR at each timepoint for both groups. The mean values, SD's, term-preterm differences and p values for the 3D measurements PCAI and wAS for both groups at each timepoint, are shown on Table 6. Table 7 shows the mean values, SD's, term-preterm differences and p values for CI at each timepoint for both groups. The absolute number of subjects diagnosed with DP in both groups at each timepoint is shown on Table 8; percentages and p values are also included. Table 9 shows the number of males and females diagnosed with DP from both groups at each timepoint.

The OCLR tended to improve over time. The values ranged from 102.30 (2.13) at 3 months to 101.92 (1.60) at 3 years and 103.66 (2.78) at 3 months and 102.19 (1.61) at 3 years for the fullterm and preterm group respectively. A statistically significant difference between the two groups was noted at the age of 3 months.

The PCAI also tended to improve over time following a similar patern to OCLR. More specifically, in the term group, the values ranged from 6.64 (5.55) at the age of 3 months to 5.89 (4.47) at the age of 3 years. In the preterm group, PCAI values ranged

from 10.91 (9.12) at 3 months old to 7.576 (3.91) at 3 years old. A statistically significant difference between the two groups was seen only at the age of 3 months. A statistically significant difference between the two groups was seen only at the age of 3 months.

The wAS in the term group showed the highest mean value (20.59 (28.12)) at the age of 12 months and the lowest (13.89 (20.87)) at the age of 3 years. In the preterm group, wAS improved over time; its values ranged from 31.31 (35.92) at the age of 3 months to 14.16 (26.07) at the age of 3 years. There was not a statistically significant difference between the two groups at any timepoint.

Finally, CI in both groups showed the lowest value at the age of 3 months and the highest at the age of 6 months. More specifically, in the term group, the mean CI values ranged from 77.20 (3.62) at 3 months to 78.30 (3.82) at 6 months whereas in the preterm group the mean CI values ranged from 75.03 (5.39) at the age of 3 months to 77.42 (6.14) at the age of 6 months; there was not a statistically significant difference between the two groups at any timepoint.

	Preterm N=34	Term N=34	p
Maternal Age, yrs	31.26 (5.73)	30.53 (5.42)	0.5886
Median Gestational Age, days (IQR)	280 (14)	233 (26)	<.0001
Male Sex, n (%)	22 (64.7)	22 (64.7)	1.0000
Singleton, n (%)	14 (41.18)	34 (100.00)	<.0001
Weight			
at Birth, g	2006.5 (712.3)	3503.8 (394.6)	<.0001
at 3 months, kg	5.94 (1.03)	6.26 (1.08)	0.215
at 6 months, kg	7.87 (1.08)	7.72 (1.07)	0.574
at 12 months, kg	9.78 (1.36)	9.79 (1.42)	0.971
at 3 years, kg	14.62 (1.70)	14.38 (1.78)	0.612
Length/Height, cm			

at birth	42.02 (4.97)	50.19 (1.72)	<.0001
at 3 months	59.07 (3.16)	61.56 (3.10)	0.002
at 6 months	67.09 (2.64)	67.48 (2.55)	0.540
at 12 months	75.22 (2.93)	76.41 (4.19)	0.185
at 3 years	94.63 (3.79)	95.45 (3.86)	0.433
Head Circumference			
at birth, cm	30.60 (3.24)	34.81 (1.30)	<.0001
at 3 months	41.16 (1.89)	41.46 (1.82)	0.499
at 6 months	44.39 (1.49)	44.09 (1.69)	0.445
at 12 months	47.38 (1.28)	47.18 (1.47)	0.544
at 3 years	50.8 (1.00)	50.7 (1.50)	.6775

Table 4. Anthropometric measurements for both groups. Mean values, +/- SD's and p values.

	Term (N=34)	Preterm (N=34)	Term-Preterm Difference	p
3 months	102.30 (2.13)	103.66 (2.78)	-1.536 (0.595)	0.026
6 months	102.25 (2.18)	102.85 (2.28)	-0.812 (0.561)	0.281
12 months	101.85 (1.72)	102.40 (2.01)	-0.685 (0.461)	0.239
3 years	101.92 (1.60)	102.19 (1.61)	-0.383 (0.428)	0.533

Table 5. OCLR: Mean values, SD's, term-preterm differences and p values.

	Term (N=34)	Preterm (N=34)	Term-Preterm Difference	p
PCAI				
3 months	6.64 (5.55)	10.91 (9.12)	-4.27 (4.18)	0.023
6 months	6.50 (5.89)	10.22 (7.84)	-3.72 (4.086)	0.032
12 months	5.81 (5.24)	8.31 (7.45)	-2.5 (3.75)	0.123
3 years	5.89 (4.47)	7.576 (3.91)	-1.686 (3.66)	0.092
wAS				
3 months	18.40 (21.86)	31.31 (35.92)	-12.903 (7.105)	0.079
6 months	19.97 (26.36)	19.18 (24.94)	0.787 (6.219)	0.901
12 months	20.59 (28.12)	14.30 (16.33)	6.286 (5.565)	0.286
3 years	13.89 (20.87)	14.16 (26.07)	-0.272 (6.291)	0.965

Table 6. PCAI and wAS. Mean values, +/- SD's, term-preterm differences and p values.

	Term (N=34)	Preterm (N=34)	Term-Preterm Difference	p
3 months	77.20 (3.62)	75.03 (5.39)	2.168 (1.097)	0.056
6 months	78.30 (3.82)	77.42 (6.14)	0.880 (1.249)	0.484
12 months	77.57 (3.68)	76.66 (5.69)	0.910 (1.195)	0.445
3 years	77.42 (3.41)	75.76 (3.91)	1.658 (0.972)	0.533

Table 7. CI for both groups. Mean values, +/- SD's, term-preterm differences and p values.

	Term (N=34)	Preterm (N=34)	p
3 months	9 (26.47)	12 (35.29)	0.4310
6 months	6 (17.65)	7 (21.88)	0.6660
12 months	5 (14.71)	6 (20.00)	0.5753
3 years	5 (14.71)	4 (16.67)	1.0000

Table 8. Number and percentage of subjects from both groups with DP at each timepoint; p values.

	Sex	Fullterm (n/N, %)	Preterm (n/N, %)
3 months	Female	3/12 (25%)	5/12 (41.6%)
	Male	6/22 (27.27%)	7/22 (31.81%)
6 months	Female	3/12 (25%)	2/10 (20%)
	Male	3/22 (13.63%)	5/22 (22.72%)
12 months	Female	2/12 (16.66%)	0/9 (0%)
	Male	3/22 (13.63%)	6/21 (28.57%)
3 years	Female	2/12 (16.66%)	1/8 (12.5%)
	Male	3/22 (13.63%)	3/16 (18.75%)

Table 9. Number and percentage of male and female subjects with DP from both groups at each timepoint.

CHAPTER 4

DISCUSSION

This longitudinal study provides data on the course of cranial asymmetry and shape from the age of 3 months to the age of 3 years in Finnish children born preterm and fullterm. 3D images were acquired at 4 timepoints (3, 6, 12 months and 3 years) using a 3dMD camera system (3dMD, Atlanta, GA). 9 outcome variables, both 2D and 3D (OCLR, ACAI, PCAI, AS, wAS, FS, EO, DD, CI) were calculated from all of the images, each representing a different aspect of cranial asymmetry or shape. In our study, diagnosis and monitoring of DP was based primarily on 2D measurement OCLR (cut off value 104.0%) and secondarily on 3D measurements PCAI and wAS (cut off value 10.5% and 24.5 respectively) as they have been shown to be the most reliable indices[96]. The measurement used for determining head shape was 2D measurement CI. Descriptive statistics of all 9 variables at each timepoint were provided, so as to describe not only the course of DP but also the variation in the cranial shape in healthy infants born preterm and fullterm. This is the first study using 3D imaging to examine the natural course of DP and the development of cranial shape in preterm and fullterm children of Finnish origin during the first three years of life.

Our results indicate improvement of cranial asymmetry in the control group (children born fullterm) between the ages of 3 months and 3 years. The point of highest prevalence was at the age of 3 months and subsequently, the incidence of DP decreased; however, cranial asymmetry was not completely resolved and there was a significant amount of cranial asymmetry present in 3-year-old children. Even though our study was

based on a population different from the populations studied previously in the literature[5, 29, 30, 32], it appears that DP follows a similar pattern worldwide.

Similarly, in the study group (children born preterm), the course of cranial asymmetry is favorable between the ages of 3 months and 3 years. In this group, the highest incidence of cranial asymmetry was also reported at the age of 3 months. In the months to follow, the prevalence of DP decreased but was still considerable at the age of 3 years. Our results are in accordance to results from previous studies reported in the literature for different ethnic groups[33-35].

The two groups had differences in regards to the correction of the asymmetry related variables. In the fullterm group, most of the correction in OCLR and PCAI occurred between 6 and 12 months of life, whereas wAS was significantly decreased from the age of 12 months to the age of 3 years. In the preterm group, OCLR and wAS was significantly decreased from 3 to 6 months of age whereas PCAI showed a significant decrease from 6 to 12 months. Our findings are not in accordance with previous literature[29, 41, 133], where it was shown that most of the correction in asymmetry related variables occurred between 3 and 6 months of life.

Mean CI values in both groups showed a similar course, with the highest mean value being reported at the age of 6 months; subsequently there was a decrease. The values calculated in the fullterm group, were lower than those previously reported in the literature[29, 117, 134] after 1992 and the implementation of “Back to Sleep” campaign by AAP. This finding is likely due to ethnic differences but different methods used to acquire anthropometric measurements could also be responsible. Comparing the mean CI values obtained from the children born preterm, was not possible since there is no previous reference in the literature.

The strengths of our study include the prospective setting and the use of 3D imaging. By following the infants from the age of 3 months, we were able to document the course of skull deformation throughout the time period when most of the resolving of cranial asymmetry occurs. Following the infants from birth with 3D imaging would have been impossible, because at that point are not able to support their head-even temporarily-so as to be scanned. In fact, achieving an acceptable head position occasionally proved challenging even with the 3-month-olds, as their shoulders were interfering in the image due to their short necks. Additionally, literature states that DP at birth is just temporary and is not associated to DP later in life[30]. However, the accuracy of the images was not affected and all landmarks were clearly identified on each image, as the 1.5ms capture time is too short for infant movement to cause any artifacts[83, 90]. Also, while point-to-point variables provide information about the cranial shape as seen from above, the volumetric variables help the reader to perceive the extend of asymmetry in the whole posterior region of the head, while the surface variables convey information about the contour, asymmetry and flatness of areas visible when looking at the occiput from behind.

The fact that cranial asymmetry was not completely resolved by the age of 3 years, raises the question about the clinical significance of DP. Unperceived asymmetry requires no treatment as an esthetic procedure. However, it is very likely that there is associated facial and mandibular asymmetry present in these infants, even though it is not perceivable to the naked eye[110, 113]. This kind of asymmetries may increase the risk of occlusal disorders and temporomandibular asymmetries[53, 110, 111] and in such a case, treating a cranial asymmetry would be of extreme importance. Unfortunately, there is not enough evidence yet so as to connect the two entities and further research is necessary.

CHAPTER 5

CONCLUSIONS

The following conclusions can be drawn from our study:

- During the first 3 years of life, DP affects preterm children more than the fullterm ones.
- The point of highest prevalence for DP is at the age of 3 months; after that, the prevalence of DP decreases.
- Most of the correction in the symmetry of the head occurred between the ages of 3 and 6 months.
- At each timepoint, more preterm than fullterm children were diagnosed with DP.
- OCLR, DP and CI had a statistically significant difference only at the age of 3 months.
- OCLR and CI increase from 3 to 6 months of age and then decrease.

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APPENDIX

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: November 2, 2016

ClinicalTrials.gov ID: NCT02283229

Study Identification

Unique Protocol ID:	EETTMK:27/2011
Brief Title:	Newborn Head Molding and Later Asymmetries
Official Title:	Newborn Head Molding and Later Asymmetries in Follow up (3D Head Shape Modelling)
Secondary IDs:	

Study Status

Record Verification:	November 2016
Overall Status:	Active, not recruiting
Study Start:	February 2012
Primary Completion:	December 2016 [Anticipated]
Study Completion:	February 2024 [Anticipated]

Sponsor/Collaborators

Sponsor:	University of Oulu
Responsible Party:	Principal Investigator Investigator: Marita Valkama [valkama] Official Title: PhD, M.D. pediatrician and neonatologist Affiliation: University of Oulu
Collaborators:	

Oversight

FDA Regulated?:	No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: EETTMK:27/2011 Board Name: Pohjois-Pohjanmaan sairaanhoitopiirin alueellinen eettinen toimikunta Board Affiliation: Pohjois-Pohjanmaan shp/ Oulu University Hospital Phone: +358-8-3155181 Email: eettinentoimikunta@ppshp.fi
Data Monitoring?:	Yes
Plan to Share IPD?:	No
Oversight Authorities:	Finland: Ethics Committee

Study Description

Brief Summary: Prospective randomized clinical interventional trial after birth in maternity ward, and follow up to 8-9 years of age.

Hypothesis: Preventive handling and caring advices to parents of newborns decrease craniofacial asymmetries (deformational plagiocephaly and torticollis). The minimum sample size of the study was calculated at 86 (43 in each arm) using a 5% significance level, a power of 80% and a fall in the prevalence of DP from 31% to 8%. Craniofacial asymmetries and appearances of occlusal defects are followed up to 9 years. 50 preterm infants can participate without intervention.

Detailed Description: The amount of craniofacial abnormal molding after birth in newborns and the frequency of plagiocephaly in infancy or later consequences of those in childhood are not known in finnish population. Head malposition and deformational plagiocephaly, however, have been linked to delayed development in early life and even much later to orthognathic problems demanding surgery in adulthood.

In this study parents with healthy newborns are randomized to have normal discharge home or discharged with extra advice information for caregivers; to charge both sided feeding and handling habits; to change regularly sleeping and lying positions; to have early tummy times.

Anthropometric measurements of the infants; tilting degrees of the head and rotations of the neck (range of movement =ROM) are taken at discharge home and at the age of 3 and 6 months, and 1, 3, 5-6 and 8-9 years. Two-dimensional digital photographs (upto the age of 6 months) and three-dimensional imaging (from the age of 3 months) are taken to measurements of the head shape (Cephalic index=CI and (approximate) Oblique Cranial Length Ratio= (a)OCLR measured using a semiautomated, computer-based method). The development quotient by Griffiths scales are assessed at the age of 3 and 6 months. Dental occlusal defect evaluation are started at the age of 3 ys.

Conditions

Conditions: Plagiocephaly

Keywords: Plagiocephaly
torticollis
occlusal defect

Study Design

Study Type: Interventional

Primary Purpose: Prevention

Study Phase: N/A

Intervention Model: Parallel Assignment

Number of Arms: 2

Masking: Single Blind (Investigator)

Allocation: Randomized

Endpoint Classification: Efficacy Study

Enrollment: 135 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Active Newborns with preventive caring advices	Behavioral: Newborns with preventive caring advices Advices to prevent head molding
Placebo Comparator: Surveillance Newborns with normal caring advices	Newborns with normal caring advices Normal handling

Outcome Measures

Primary Outcome Measure:

1. Presence of Plagiocephaly (The number of children in groups with plagiocephaly (CI, OCLR =/> 104%)
   [Time Frame: 3 months] [Safety Issue: No]
   The number of children in groups with plagiocephaly (CI, OCLR =/> 104%)

Secondary Outcome Measure:

2. Severity of plagiocephaly
   [Time Frame: 3 months] [Safety Issue: No]
   The number of children in groups with plagiocephaly as mild; aOCLR 104-107%; moderate 107-111%; severe =/>111 %
3. Change in plagiocephaly
   [Time Frame: From 3 to 6 months] [Safety Issue: No]
   The number of children in groups with plagiocephaly as mild; aOCLR 104-107%; moderate 107-111%; severe =/>111 %
4. Occlusal defects (The number of children in groups with occlusal defects)
   [Time Frame: 6 years] [Safety Issue: No]
   The number of children in groups with occlusal defects
5. Change in occlusal defects
   [Time Frame: from 6 years to 9 years] [Safety Issue: No]
   The number of children in groups with occlusal defects

Other Pre-specified Outcome Measures:

6. Development (Development quotients by Griffiths scales in groups)
   [Time Frame: 3 months] [Safety Issue: No]
   Difference in Development quotients by Griffiths scales in groups
7. Change in Development (Development quotients by Griffiths scales in groups)
   [Time Frame: From 3 months to 6 months] [Safety Issue: No]
   Difference in Development quotients by Griffiths scales in groups

Eligibility

Minimum Age: 1 Days

Maximum Age: 6 Days

Gender: Both

Accepts Healthy Volunteers?: Yes

Criteria: Inclusion Criteria:

- 1-6 days after birth;
- Healthy newborns in maternal ward, and living in near by Oulu region.
- Preterms at the age of 34-44 gestation weeks in near by Oulu region (non randomized)

Exclusion Criteria:

- Congenital anomalies,
- Very early discharge,
- Parental refusal

Contacts/Locations

Study Officials: Pertti Pirttiniemi, Professor
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References

Citations: [Study Results] Aarnivala HE, Valkama AM, Pirttiniemi PM. Cranial shape, size and cervical motion in normal newborns. Early Hum Dev. 2014 Aug;90(8):425-30. doi: 10.1016/j.earlhumdev.2014.05.007. PubMed 24951081

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Links: