The effect of spinopelvic parameters on the development of proximal junctional kyphosis in early onset scoliosis

Kubat, Ozren

ZAGREB UNIVERSITY
SCHOOL OF MEDICINE

Ozren Kubat

The effect of spinopelvic parameters on the development of proximal junctional kyphosis in early onset scoliosis

DISSERTATION

Zagreb, 2021.

ZAGREB UNIVERSITY
SCHOOL OF MEDICINE

Ozren Kubat

The effect of spinopelvic parameters on the development of proximal junctional kyphosis in early onset scoliosis

DISSERTATION

Zagreb, 2021.

This dissertation was made at the

Department of Orthopaedic surgery, Clinical Hospital Centre Zagreb, Croatia
Pediatric Orthopedic Department, Izaak Walton Killam Health Centre, Halifax, Canada
Hospital for Special Surgery, New York, United States of America

Mentor: Domagoj Delimar, MD, PhD
Co-Mentor: Ron El-Hawary, MD, PhD

Mojoj Obitelji. Ovo je za sve Vas.
"A society grows great when men plant trees whose shade they know they shall never sit in." – ancient Greek proverb

TABLE OF CONTENTS

LIST OF ABBREVIATIONS (in alphabetical order)

AIS – adolescent idiopathic scoliosis

ASD – adjacent segment disease

C – cervical

CA – Cobb angle

CL – cervical lordosis

CSSG – Children's Spine Study Group

ERC – external remote controller

EOS – early onset scoliosis

EOSQ-24 – Early Onset Scoliosis Questionnaire-24

GR – growing rod

GSSG – Growing Spine Study Group

HGT – halo gravity traction

HRQOL – health related quality of life

ISSG – International Spine Study Group

LIV – lower instrumented vertebra

L – lumbar

LL – lumbar lordosis

MCGR – magnetically controlled growing rod

PA – posteroanterior

PI – pelvic incidence

PJA – proximal junctional angle

PJK – proximal junctional kyphosis

PT – pelvic tilt

RR – relative risk

SD – standard deviation

SRS – Scoliosis Research Society

SS – sacral slope

T – thoracic

TGR – traditional growing rod

TK – thoracic kyphosis

TLSO – thoracolumbosacral orthosis

UIV – upper instrumented vertebra

VEPTR – vertical expandable prosthetic titanium rib

1. Introduction

1.1. Scoliosis

1.1.1. Definition, classification, etiology

The term *scoliosis*, derived from the Greek word meaning „crooked“, was first used as in regard to spinal deformities by the Father of Medicine, Hippocrates (460–370 BC).[1,2] However, in his works the term is given a generic meaning, referring to almost any type of spinal curvature. One of his successors, Galen of Pergamon (129-210 AD) commented on Hippocrates' flawed use of the term, and described four types of spinal deformities – kyphosis when the spine moves backwards, lordosis when propelled forward, scoliosis as it shifts to the side and succussion, a situation without any deformity but with movement of the intervertebral articulations.[3] So, it was Galen who is credited for the first use of this term as it is used today.

Modern orthopaedic surgery defines scoliosis as a lateral deviation of the spine greater than 10 degrees measured on a posteroanterior (PA) radiograph. This method of measuring was introduced by John R Cobb in 1948.[4] Appreciating the three-dimensionality of scoliosis is essential in being able to understand its effect on the body, as well as to recognize factors important to successful treatment.

This is a complex deformity, comprising changes in all three anatomical planes; lateral shift in the coronal (frontal) plane, straightening in the sagittal (lateral) and rotation around the vertebral axis in the axial (transverse) plane. The most significant changes are located in the apex of the curve, and as the deformity progresses it leads to structural changes of the vertebra and rib cage.

Scoliosis is usually classified according to curve location, age of onset and etiology. Curve types are designated by the apical vertebra – the vertebra most deviated laterally from the vertical axis that passes through the center of the patient's sacrum. According to the curve location, we discern between cervical (C) (apex between C1-C6/C7 disc), cervicothoracic (apex between C7-T1), thoracic (T) (apex between T2-T11/T12 disc), thoracolumbar (apex between T12-L1) and lumbar (L) (apex between L2-L4/L5 disc) scoliosis. According to age of onset, infantile scoliosis appears in children younger than (and including) three years of age, juvenile in those aged four to (including)10 years old, adolescent from 11 – 18 years, and adult from 18 years of age onwards.[5] Etiology of scoliosis can be idiopathic, congenital, neuromuscular, syndromic, degenerative and hysteric.

1.1.2. Early Onset Scoliosis

According to the foremost authority on the patient of scoliosis, the Scoliosis Research Society (SRS), early onset scoliosis (EOS) is any scoliotic deformity in children from birth until the age of 10 years.[5] Etiologies of EOS can vary, being mainly congenital, syndromic, neuromuscular and idiopathic.

The importance of this pathologic entity comes from the fact that spinal deformity occuring in these (very) early years of life can compromise growth and expansion of the thoracic cavity and lungs, creating so called thoracic insufficiency syndrome.[6] This brings upon these patients a higher risk of respiratory morbidity and mortality, and validates classifying EOS as a separate group, due to this uniform and unique risk to their life. In these patients, as opposed to those with adolescent onset of scoliosis, a significantly higher mortality rate has been reported, as well as the fact

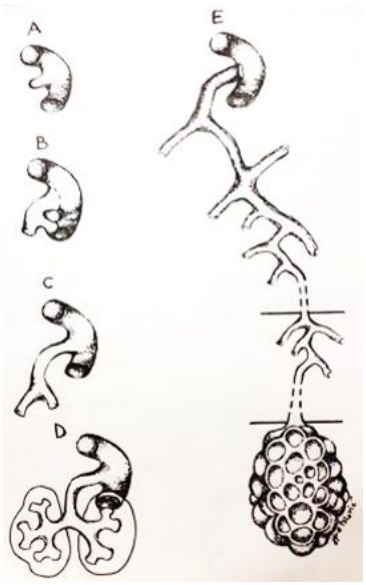
that increasing deformity equals decrease in the patients' vital capacity.[7-9] There are two main reasons for respiratory failure in EOS patients: intrinsic alveolar hypoplasia and extrinsic disturbance of chest wall function.

1.1.3. Lung development, thoracic growth and the detrimental effects of EOS

The human respiratory system develops through five stages: embryonic, pseudoglandular, canalicular, saccular and alveolar (Figure 1).[10] Embryonic stage takes place during weeks four to seven of organogenesis, and involves formation of the lung bud, its separation from the primitive gut and branching into two buds – one for each lung. The end of week seven marks the beginning of the pseudoglandular phase, with each lung resembling a small tubulo-acinar gland.[10] During weeks seven to 16, repetitive sprouting and bifurcation of the lungs takes place by the process of „branching morphogenesis“. Together with this new growth and division, another process takes place in this phase – growth and differentiation of the primitive epithelium, going from proximal to distal.[11] The canalicular stage takes place during weeks 16-25 of gestation. It is marked by formation of the air-blood barrier and secretion of surfactant. There is increased pulmonary vasculature development, with vessel proliferation and formation of a capillary network around the alveolar epithelium.[12] Saccular stage, spanning weeks 24–38, correlates with the earliest viability period of the human fetus.[10] In this stage, primitive terminal air spaces are formed (alveolar ducts and sacs), and type two cells, formed during the canalicular stage, start producing surfactant. Pulmonary parenchima keeps increasing in size, and the surfactant system matures further. The surfactant production begins in the 26th

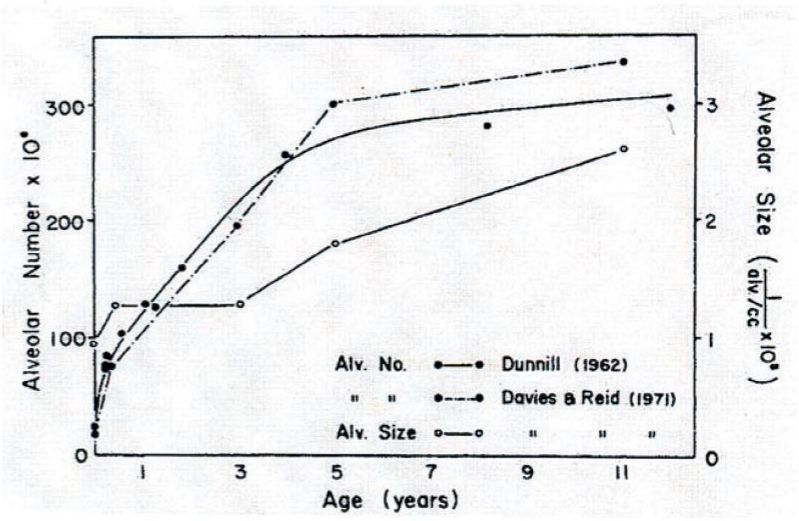
week of gestation, and slowly progresses from there, while around 30 weeks of gestation it starts being secreted into the airway lumen and lines the alveoli.[13] The saccular stage is also marked by a spike in fetal cortisol concentrations, which helps further maturation of the lungs by increasing synthesis and secretion of surfactant as well as differentiation of alveolar epithelial cells.[14,15] The alveolar stage starts just prior to birth and extends to the first few years of a child's life. The main processes that mark this stage are secondary septation (division of alveolar ducts into terminal alveoli) and pulmonary angiogenesis to maximise the gas exchange area of the lungs. With the number of airway generations reaching their total at time of birth, there is still great change to the morphology of the pulmonary parenchima.

Figure 1. Schematic presentation of human lung development. A) Primitive lung anlage emerges as the laryngotracheal groove from the ventral surface of the primitive foregut B) Separation of primitive trachea from the primitive esophagus C) Separation of the embryonic larynx and trachea with the two primary bronchial branches from the embryonic esophagus D) The primitive lobar bronchi branching from the primary bronchi E) A schematic rendering of the airway at term. (Artwork by Jasmina Petrović)



Over 85% of the alveoli form after birth.[13] The vascular growth continues at an accelerated rate throughout this phase, in proportion to formation of new alveoli, which together help expand the lung gas exchange surface. After 18 months of age this number of new vessels slows with alveolar growth.[16] It is now believed that the final phase of alveolar formation (manifesting as growth of all lung components) continues until the time the long bones stop growing, making normal respiratory function especially dependent on the completion of these postnatal steps in lung development.[10] At functional maturity, there are approximately 300x10^6 alveoli in the lungs. This number is achieved by the age of eight, with the „golden period“ of maximal growth occuring before five years of age (Figure 2), while the hypertrophy carries on until the completion of bony thorax growth.[17-25]

Figure 2. Graph showing the increase in number and size of alveoli with age using quantitative analysis according to Dunnill (1962)[17] and Davies and Reid (1971)[19]. Note the steep increase of the graph lines up to the age of five years, indicating the maximal increase in number of alveoli in children, the so-called “golden period” for lung development.



During this marked alveolar hyperplasia, not only are the lung tissues growing, but the cage which contains them experiences rapid growth as well. Failure of alveolar multiplication (intrinsic alveolar hypoplasia) is most likely the dominant source of respiratory failure in EOS patients, because the deformity of the spine and thorax prevents lung tissue hyperplasia. This has been corroborated by studies investigating lung tissue acquired by biopsies.[20,26-28] The alveoli found in such compromised lungs uniformly present as hypertrophied, most likely as a form of compensatory effort. The bony thorax, built out of thoracic vertebrae, ribs and the sternum increases in both length and circumference, very much so during puberty as the „third micropeak of puberty“ according to DiMeglio et al.[29] The thoracic spine grows six cm (increases by 50%, from 12-18 centimeters) in the first five years of life, reaching around 60% of the final, adult length by this age.[30] When it comes to thoracic volume, at birth it equates to approximately six percent of the adult volume, increasing to 30% at five years, 50% at the age of 10 and reaching 100% at the age of 15.[29] It is easy to note that the „golden period“ of lung development coincides with the rapid growth of the thoracic spine and rib cage.

Deformities of the thorax associated with scoliosis produce its functional incompetence, resulting in the extrinsic disturbance of chest wall function.[31,32] This incompetence of the chest wall is best seen and most pronounced in patients with rib anomalies which often accompany congenital scoliosis. In these patients ribs can often be fused, blocking normal chest movement during respiration, or absent, resulting in a localized „flail“ chest or paradoxical chest segment. When compared to idiopathic scoliosis at the same magnitude of Cobb angles (CA), patients with congenital scoliosis had decreased vital capacity, most likely due to the associated rib anomalies which disturb normal respiration.[33] The ribs do not necessarily have to be anomalous,

fused or absent, in order to influence respiration. In noncongenital deformities scoliotic curves result in rib deformity which also negatively impacts respiration. On the concave side of the curve, ribs are pressed closer together narrowing the intercostal spaces and restricting the end-inspiratory volume, while on the side of the convexity, intercostal spaces are widened and unable to support normal expiratory function.[34]

1.1.4. Treatment options

Non-operative treatment

The most important premise of EOS treatment is delay of surgery, if possible by the age of 10, using nonoperative techniques in order to try and minimize the risk of thoracic insufficiency. It has been demonstrated in the literature that most patients (74% - 92%) with idiopathic infantile EOS spontaneously resolve.[35,36] For those who need it, the three methods of non-operative treatment used are casting, bracing and halo gravity traction (HGT).

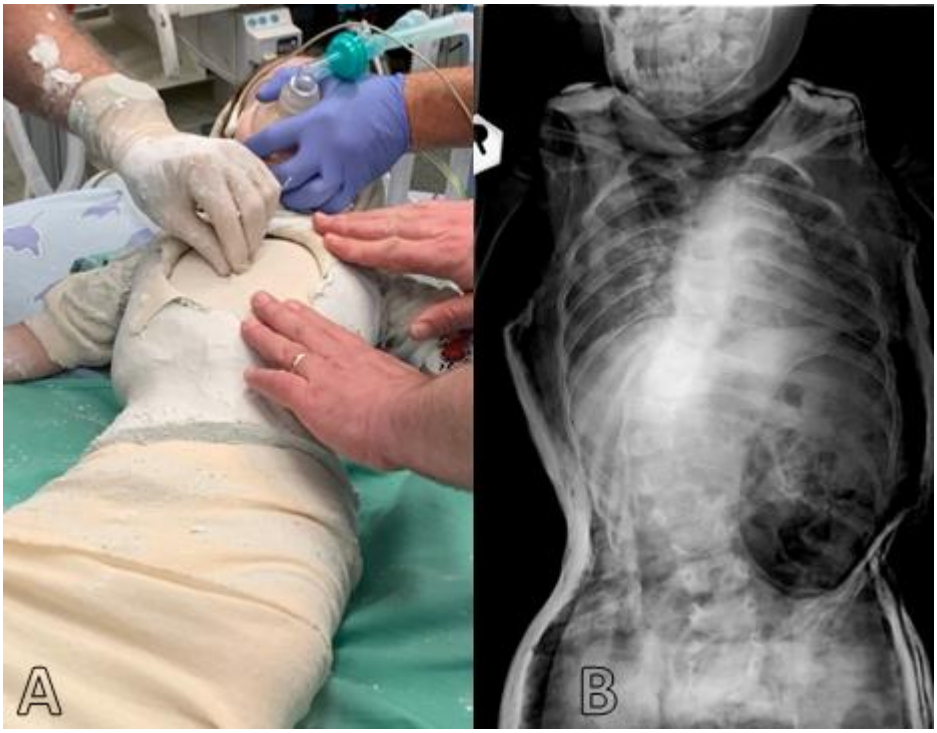
Casting

The technique of corrective casting for scoliosis was first described by Sayer in 1877,[37] with the goal of the early history of casting being to reduce curves prior to surgery and maintain correction postoperatively by the so-called turnbuckle cast in the setting of uninstrumented fusions established by Hibbs et al.[38] Patients could not ambulate in a turnbuckle cast, so in an attempt to improve the therapy, Risser developed „localizer casting“.[39] Cotrel and Morel further enhanced Risser's technique and gave us the E(longation) D(erotation) and F(lexion) casting, which is still used to this day.[40] The authors of this traction, derotation and bending casting technique made a bold suggestion that it could correct infantile scoliosis. However, with the advent of successful surgical options in the form of Harrington's spinal instrumentation, casting fell out of favor for managing adolescent scoliosis.[41] Some centers kept the casting

tradition and knowledge alive, and after reports by Mehta et al. and Sanders et al. there was a worldwide resurgence of interest in these methods.[42,43]

Casting provides a non-removable and well-fitting jacket which exerts constant corrective forces on the growing spine. It also removes family compliance from the equation, as the parents are unable (unless very resourceful and persistent) to remove the cast. Today, the golden standard for casting patients with scoliosis is by using a specialized traction table. The patient is under general anesthesia, positioned supine, with a head halter and pelvic traction. The table provides support for the entire weight of the child by means of straps, keeping the thorax, shoulders and pelvis free for manipulation and application of the cast. Correction is achieved through traction and manipulation of the curve, putting pressure on the exact points predetermined both clinically and on the patient's radiographs (Figure 3).

Figure 3. Elongation, derotation and flexion (EDF) casting. A) A clinical depiction of a finished EDF cast. The procedure is performed under general anesthesia on a specialized table which allows access to the entire patient's spine while still safely supporting the body. Note the opening of the abdominal hole for easier breathing and feeding. (Courtesy of Dror Ovadia, Tel Aviv) B) Standing posteroanterior (PA) radiograph of the spine in a patient with the EDF cast in place. Note the shoulder straps as well as the emphasized molding on the waist of the patient which help keep the cast in place. (Personal archive).



A well done cast corrects the scoliotic curve by rotating and shifting it to the midline, while avoiding pressure on the ribs and pushing them toward the spine.[44] Casts are changed in intervals of two to four months, depending on the age and growth rate of the child. Casting is usually performed for up to one year, after which a period of brace wearing is instituted followed by more casting. Many centers use their own timing algorithm, but usually the period of brace wear is about six months after which the cast is reinstated. This is done until either resolution of the curve is achieved, or, in case of unresolved curves, an age favorable for surgery is reached. Casting can also be discontinued, if obviously failing.[44]

Casting has its complications, the main acute ones being superior mesenteric artery syndrome and neurologic dysfunction particularly affecting the cranial nerves and the brachial plexus. In the longer term, pressure sores over bony prominences can develop.

Bracing

Bracing has been proven effective in the treatment of adolescent idiopathic scoliosis (AIS), but there are no studies to prove its efficacy for EOS.[44] Notwithstanding, it is the most common nonsurgical treatment for EOS. Bracing is undoubtedly more convenient for both the patient and family, because a brace can be taken off for hygiene purposes and activities. However, this feature of brace treatment has its down sides, as by removing the brace for a certain amount of time a day, the corrective effect on the curve(s) cannot be constant. Also, with the main function of bracing being to stabilize the deformity, it is not as effective in permanent deformity correction as is casting. Most commonly, braces used in treatment are modifications of a custom-molded thoracolumbosacral orthosis (TLSO). Fitting a brace in young children is challenging, mostly due to their inherently poor compliance during measuring and molding, as well as their anatomical peculiarities (such as a typically large abdomen in infants and toddlers). Also, with their skeletons being more flexible and pliable, a standard three-point bend brace can exert too much pressure on the ribs and produce additional chest wall deformity. In the case of EOS, it is especially important for a brace to enable a three-dimensional deformity correction to boost the correction of the chest wall, instead of only focusing on correcting the scoliosis CA.

Halo gravity traction

HGT was first described by Stagnara.[45] It is an important ancillary tool in EOS treatment, that can be utilized either prior to casting or before surgery. The function of HGT is to accustom the spinal cord to the gradual correction, thereby making any

subsequent treatment safer, temporarily decrease the curve, improve preoperative respiratory dynamics by achieving an upright thorax, and even provide nutritional improvement preoperatively.[44] It is indicated in those patients whose curves are stiff and very large (usually >90°), kyphoscoliosis and decreased pulmonary or nutritional status.[46] The usual technique in EOS is to use multiple pins (six to eight) as anchors attached to the anterior and posterolateral parts of the lamina externa of the skull, start with light traction and increase gradually.[47] The amount of traction usually can exceed 50% of body weight. Complications are not common, and can include changes in neurologic status, hypertension, cranial nerve dysfunction, especially cranial nerve VI with resulting diplopia (with an incidence of 0.07%).[48]

Surgical treatment

Moe et al. were the first to use a subcutaneous Harrington instrumentation in young children with otherwise uncontrollable scoliotic curves, anchored only in the top and bottom, in order to correct the scoliosis but still provide growth.[49] The group reported on the early cases and found the apex was unfused, while the end vertebrae of the constructed fused spontaneously.[49] However, consecutive reports have shown that the unexposed segments also experienced spontaneous fusion to a certain degree, although they had been left untouched.[50]

After the initial reports, improvements to the technique were made, such as subfascial rod placement to try and minimize overlying skin issues, dual-rod technique for additional stability.[51,52] Building on the pioneering works of the original generation of spinal surgeons, the strategy in surgical treatment of EOS patients has improved significantly with better understanding of the biomechanics of the developing spine

under treatment and the use of modern growth-friendly implants. These implants are classified into three types: distraction-based, guided growth and compression-based implants.[53]

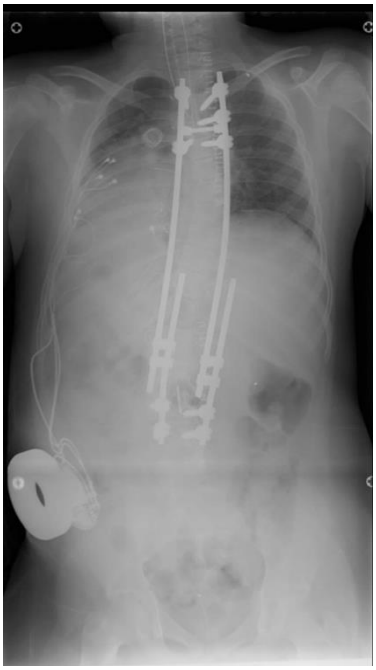
Distraction-based implants

Today, this type of implant is most commonly used in treatment of EOS.[53] Expandable rods are anchored only to the upper and lower parts of the curve, after which they are periodically extended to apply distraction to the spinal column as the child grows. There are four types of distraction-based implants: traditional growing rod (TGR), vertical expandable prosthetic titanium rib (VEPTR), hybrid systems and magnetically controlled growing rod (MCGR).

TGR uses hooks and/or screws for the proximal and distal vertebral anchors, while the rods that connect them are placed subfascially (Figure 4). Leaving most of the spine unexposed and unfused allows for motion and growth in between the anchors. The construct is then serially lengthened by repeat surgeries, usually at approximately six month intervals. Akbarnia et al. reported on 1.2 cm of growth in T1 – S1 length per year at a mean four–year follow–up by using TGR.[52] Akbarnia et al. also demonstrated that shorter intervals in between lengthenings allowed for significantly higher T1–S1 growth rates of 1.8 cm/year.[54]

Figure 4. One month postoperative anteroposterior radiograph of a child with early onset scoliosis (EOS) who underwent traditional growing rods (TGR) implantation. In this specific case, the presence of a heart stimulation device precluded the use of

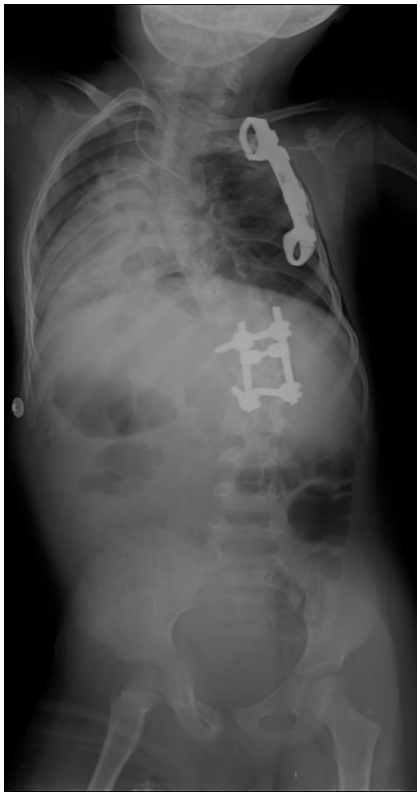
magnetically controlled growing rods (MCGR) in the spine so the surgeon opted for a TGR construct. (Courtesy of Dror Ovadia, Tel Aviv)



VEPTRs use ribs as anchors, although sometimes they can be attached to the spine or pelvis as well. The primary idea behind the concept is to provide thoracic expansion in cases of rib cage deformities (Figure 5). Same as TGR, VEPTRs undergo repetitive surgical extensions. This type of treatment has exhibited consistent growth of the spine with serial extensions (mean 71 mm across four lengthenings, one every 6 months) while improving the scoliotic curve in the frontal plane.[55,56]

Figure 5. Three months postoperative anteroposterior radiograph of an early onset scoliosis (EOS) patient treated for congenital scoliosis and thoracic insufficiency syndrome by multiple osteotomies of fused ribs of the right hemithorax and implantation of the vertical expandable prosthetic rib (VEPTR) as well as short fusion

of the thoracolumbar transition following hemivertebra excision. (Courtesy of Dror Ovadia, Tel Aviv)



A hybrid distraction-based construct utilizes ribs as anchors on the proximal end of the construct, while the distal end is placed on the spine as in TGR. By avoiding rigid fusion of the proximal vertebral anchors, growth of those segments is enabled. Another benefit to this is the fact that the use of hooks on ribs reduces rigidity of the entire construct. Decreased rates of rod breakages by using this technique have been reported in the literature.[57]

MCGR technique consists of telescoping rods which contain an internal magnet that is controlled by an external remote controller (ERC) (Figures 6 and 7). It has enabled orthopaedic surgeons to perform outpatient lengthenings, without the use of (repetitive) anesthesia or pain medication. It is most often used as a purely spine-

based instrumentation, but can also be set up as a hybrid, connecting the distal spinal anchors to the proximal rib anchors. This form of „non-invasive“ lengthening allows the surgeon to lengthen more often, mainly every two to three months, as opposed to six months per lengthening of TGRs.

Figure 6. Three month postoperative anteroposterior and sagittal postoperative radiographs of a patient with early onset scoliosis (EOS) treated with implantation of magnetically controlled growing rods (MCGR). (Courtesy of Dror Ovadia, Tel Aviv)

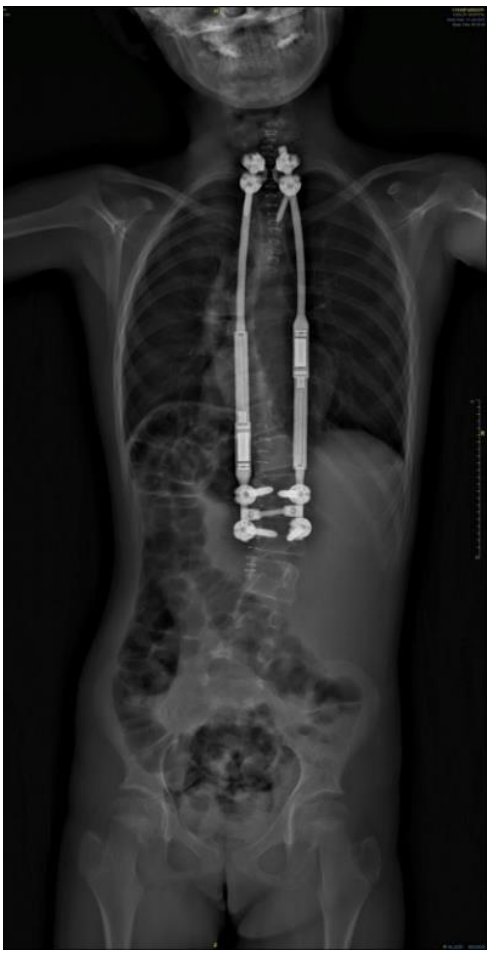


Figure 7. The external remote controller (ERC) (NuVasive Inc., San Diego, USA) for the magnetically controlled growing rod (MCGR) distraction. The procedure is

performed every two months in an outpatient setting, without the use of analgesia or sedation as it is quick and pain free. The patient is in a prone position with a pillow beneath the abdomen so as to flex the spine slightly in order to bring it closer to the device. The ERC is held firmly against the skin and the operator starts the magnetic rotors through a push of a button, at the same time looking at the digital display showing the amount of elongation, aiming for two to three millimeters at a time. (Personal archive)

1.2. Radiographic spino-pelvic parameters

Human evolution to upright posture and bipedalism caused extensive modifications in our skeletal morphology.[58] The „pelvic vertebra“, which is the very foundation of spinal balance, was paramount in this evolution. Progressive remodelling in terms of widening and retroversion of the pelvic ring allowed humans to achieve erect posture.[59] It was those modifications that have driven the spino-pelvic transformation from a primitive sagittal „C-shape“ to the „S-shape“ with cervical, thoracic and lumbar curves. No other species has spinal alignment that includes a lumbar lordosis (LL).[59] These changes enabled us to adopt a neutral upright posture with minimum energy expenditure. Dubousset brought this concept to the attention of the medical community, with his theory on the „conus of balance“, which refers to a narrow range of standing alignment where the body remains balanced with minimal muscle action.[60]

1.2.1 Regional curvatures of the spine in the sagittal plane

All of the following parameters are measured using the Cobb method, proposed by John Robert Cobb in 1948.[4] These curvature metrics are very much interdependent, and it must be noted that there will be noticeable variation in the normal values reported in the associated literature both for adults and children alike.[61-63]

Cervical lordosis

The most common method to determine cervical lordosis (CL) is by measuring the lordosis angle from the upper endplate of C2 vertebra to the lower endplate of C7 vertebra.[64] Reported lordosis values on asymptomatic patients vary from 15°±10° in young adults to 25°±16° in patients over 60 years old, but there are also several reports of kyphotic sigmoid cervical alignment in asymptomatic patient (as many as 13-34%).[65,66]

Thoracic kyphosis

Thoracic kyphosis (TK) is most commonly defined as the angle between the upper endplate of T5 vertebra and the lower endplate of the T12 vertebra. The average normal values of T5-T12 TK in asymptomatic patients vary from 10° to 40°.[67]

Lumbar lordosis

The lumbar curvature specific to humans is paramount to upright posture.[68] The LL is defined as the angle between the endplate of the sacrum and the cranial endplate of the transitional vertebrae located between the lumbar curve and thoracic curve, usually the T12 vertebra. It is important to note that up to two thirds of the total LL value comes from the lower lumbar segments (i.e. L4-L5 and L5-S1). Mean reported values for L1-S1 LL in asymptomatic patients vary from 40° to 60° (standard deviation (SD) around 10°), with extreme values ranging from 30° to 80°.[67]

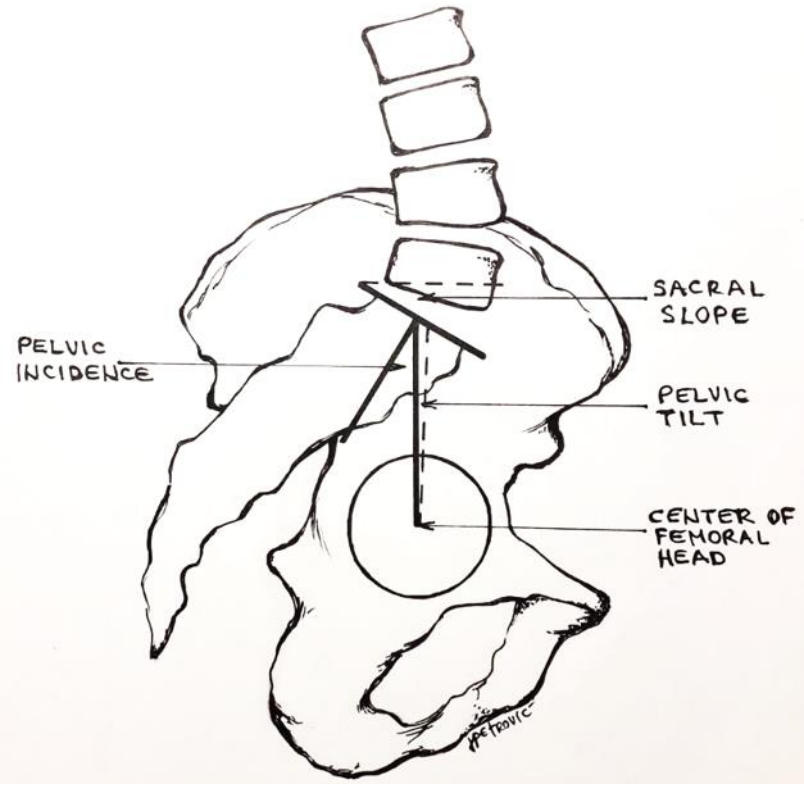
1.2.2. Spinopelvic parameters

The early 1990s brought about a new concept of the “pelvic vertebra”, which prompted numerous investigations on the way pelvic morphology influenced spinal alignment. Duval-Beaupere et al. came up with three relevant parameters to use when evaluating the pelvis: Pelvic Incidence (PI), Pelvic Tilt (PT), and Sacral Slope (SS) (Figure 8).[69] These three parameters are interrelated by the following geometrical formula:

$$PI = PT + SS.$$[69,70]

The pelvis provides a critical link between the spine and the lower extremities and can be seen as the regulator of the sagittal plane.[71]

Figure 8. Depiction of the sagittal spinopelvic parameters, which can be measured in the erect position as well as sitting down in non-ambulatory patients, showing: Pelvic incidence (PI) – the angle between a line drawn from the center of the femoral head axis to the midpoint of the sacral plate and the perpendicular to the sacral plate. Sacral slope (SS) – the angle between the horizontal and the sacral plate. Pelvic tilt (PT) - the angle between a line drawn from the center of the femoral head axis to the midpoint of the sacral plate and the vertical. (Artwork by Jasmina Petrović)



Pelvic incidence

The PI is a fixed anatomical parameter which defines the relative orientation of the sacrum versus the ilium.[69,70] In adulthood due to the limited motion of the sacroiliac joints, PI is considered a morphological parameter, not affected by the orientation of the pelvis. It is important to note that, although the general rule is that the pelvis is morphologically stable throughout a person's life, it changes shape as a person transitions from the fetal to the neonatal stage, and changes again in the transition to adulthood before stabilizing.[72-74] The reported average PI value in asymptomatic adult patients is 52°±10° with lower values around 35° and higher ones near 85°.[61] Studies on patients of age from four to 18 demonstrated mean value of 45° in patients under 10 years of age, and 49° in patients over 10 years of age.[72,73] As the pelvis „drives“ the spinal curves, the effect of PI is such that asymptomatic patients with a small PI

tend to have a vertically positioned sacrum with a small and short LL. Those with large PI values tend to have a more horizontal sacrum and a large and long LL.

Pelvic tilt and sacral slope

The pelvis is free to rotate around the femoral heads; its angular orientation in the sagittal plane (a.g. anteversion and retroversion) can be assessed by the SS and the PT. These two parameters are directly related by the geometrical equation

$$PI = PT + SS.$$[71]

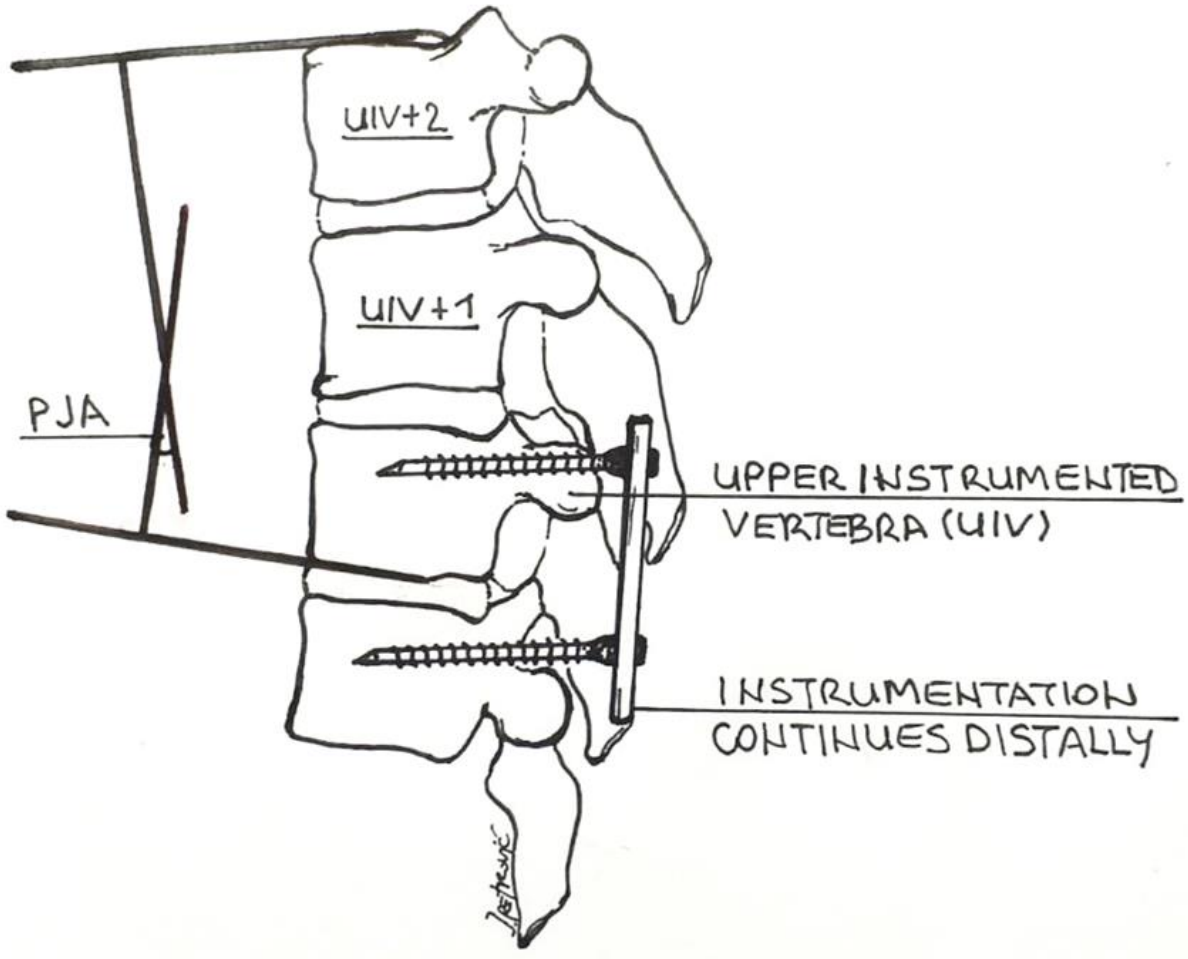
The SS depicts the sagittal inclination of the sacral endplate. The average SS value in asymptomatic patients has been reported to be 41°±8°.[61,73] SS is affected by patient positioning, making it a positional parameter.

The PT is a dynamic parameter that also changes with pelvic rotation about the hip axis. The average PT in asymptomatic adults has been reported to be 13°±6°. Like PI, PT increases during childhood, and studies on children have shown that they exhibit a smaller PT at the age of seven years old (PT = 4°), than they do as adolescents (8° in 13 year old patients).[72,73] Positive values of PT denote a posterior rotation of the pelvis (e.g. retroversion), and negative values denote an anterior rotation (e.g. anteversion).

1.2.3. Proximal junctional kyphosis

Proximal junctional kyphosis (PJK) is a non-physiologic, sagittal plane angulation that occurs cephalad to an instrumented spine. In adults and adolescents, proximal junctional failures above deformity constructs have been well established with different risk factors identified; however, the incidence, nature and clinical significance of this kyphosis remains unclear. Several reports in the literature have shed light on PJK in adults and adolescents with variable definition, incidence, prevalence, acuteness, risk factors, clinical significance and the need for revision surgery. The most consistent proximal junctional angle (PJA) measurement in the literature as outlined by Glattes et al. has been between the caudal endplate of the upper instrumented vertebra (UIV) and the cephalad endplate of two levels above the UIV (Figure 9), with abnormal PJK defined as having proximal junctional CA ≥ +10° and at least 10° greater than the pre-operative measurement.[75] Kim et al. conducted a systematic review on PJK after spinal deformity fusion surgery in which they were able to include seven studies according to their selection criteria, all sharing the aforementioned definition.[76] They reported a PJK incidence of 17%-39%, mostly noted by two years postoperative, with a moderate level of evidence. Risk factors included increased age, fusion to the sacrum, combined anterior and posterior spinal fusion, thoracoplasty, UIV at T1–T3, and non-anatomic restoration of TK. The type of implants used at the proximal level did not have a consistent statistically significant association with PJK across studies. The authors also concluded that PJK does not seem to have a detrimental effect on health related quality of life (HRQOL) outcomes, at least in milder/non-revision forms.

Figure 9. Graphic depiction of the proximal junctional angle measurement, as designed by Glattes et al.[75] The upper instrumented vertebra (UIV) is the one at which the instrumentation ends in its proximal part. The angle of the proximal junction was measured between the lower endplate of the UIV and the upper endplate of the second vertebra above it (UIV+2). (Artwork by Jasmina Petrović)



1.3. Registries

Data from two registries were used for this research project, the Children's Spine Study Group (CSSG) and the Growing Spine Study Group (GSSG). They include operative and non-operative care, as well as natural history cases. Both registries are based in the United States of America (CSSG – Valley Forge, Pennsylvania, GSSG – San Diego, California), and at the time of the study they gathered expert pediatric spine surgeons from 30 countries. At the time of the study the CSSG was chaired by Mr. Jack Flynn, and the GSSG Chairman was Mr. Behrooz Akbarnia.

The registries are charitable, non profit organizations receiving funding from private donations and industry support. They received support from following companies: DePuy Synthes Spine, NuVasive, Zimmer Biomet, Medtronic, OrthoPediatrics, Globus Medical Inc. and Stryker.

Data input is performed by the respective Institution, and a centralized analyst reviews the data regularly for quality control. Audits are performed at regular intervals to ensure data quality.

1.4. Health related quality of life

HRQOL is an individual's or group's perceived physical and mental health over time. It is a health assessment tool and helps improve quality of life through various indicators. On the individual level, it includes perceptions of physical and mental health, while on the level of a group it includes community-level conditions, resources,

policies, and practices that influence a population's health perceptions and functional status.

1.5. Purpose of doctoral thesis

In order to avoid sequelae of early spinal fusion, many techniques have been developed to manage deformity of the spine in children with EOS.[52,77-81] Posterior distraction-based implants, such as rib-based and spine-based growing rods (GR), are commonly used as a form of surgical treatment for this heterogeneous population. Periodic posterior distraction across the deformity helps in stabilization of the deformity, while still allowing for growth of the spine and for more space available for the lungs. It is known that intra-operative posterior distraction forces are kyphogenic by nature and may predispose patients to the development of hyperkyphosis and/or PJK.

PJK has only recently been studied in the EOS population. Li et al. studied 68 patients treated with the VEPTR and determined that PJK developed in six percent of patients; risk factors including pre-operative thoracic hyperkyphosis and the presence of weak paraspinal muscular support in neuromuscular patients.[82] Reinker et al. found in 14 patients that upper cradle placement below the third rib, distal anchor placement at too proximal a level, resulting in a shortened lever arm and less power in the implant, and recurrent erosion and loss of fixation on the proximal ribs contributed to progression of TK.[83] Shah et al. reviewed 43 patients and reported how lengthenings of the GR systems do not cause deterioration in the sagittal plane parameters over time, and stress that PJK is a potential complication of this procedure that has to be anticipated.[84]

Spinopelvic morphology plays a critical role in the balanced upright posture and failing to account for it in treating spinal deformity increases the risk for residual spinal deformity and treatment failure. Research of spinopelvic morphology and its influence on sagittal spinal geometry and patient outcome in both pediatric and adult patients has become recognized to a greater extent over the last decade.[72,73,85-92] The International Spine Study Group (ISSG) has established several links between sagittal plane spinopelvic alignment and the development of PJK in adult scoliosis. They have introduced several novel concepts, such as age-adjusted surgical correction goals and thoracic compensation that help to identify risk for development of PJK.[91-93] These concepts have not yet been studied in young children with scoliosis.

CSSG has performed studies in an effort to establish sagittal plane spinopelvic alignment in children with EOS and to determine the effect of surgical treatment on these parameters. The initial study performed on 80 children with scoliosis established baseline values for spinopelvic parameters for young children with scoliosis and compared these values to children without spinal deformity. Spinopelvic parameters were found to be the same, except for a significantly greater PT and a significantly lower SS in children with scoliosis. These values are now used as a baseline values for both the natural history and for assessment of radiographic outcomes after surgical intervention in children with EOS.[94] In a separate study, which analyzed 79 patients, the group compared the effects of rib-based vs. spine-based distraction on sagittal spinopelvic parameters and found that, at minimum two-year follow-up, patients treated with rib-based implants had greater CL, greater TK, less LL, less SS, greater PT, and less pelvic radius angle as compared to those treated with spine-based implants. As it was found that rib-based and spine-based implants resulted in different post-operative sagittal profiles, the patient's pre-operative sagittal alignment should be

considered when deciding upon which type of distraction-based growing system to use for an individual patient with EOS, for example thoracic hyperkyphosis precluding from use of rib-based instrumentation.[95]

The CSSG has also performed studies examining the risk of developing PJK in EOS patients. This includes a multi-center, retrospective, radiographic comparison for a group of 40 children with EOS who were treated with posterior distraction-based implants.[96] Twenty percent at immediate post-operative follow-up and 28% at minimum two-year follow-up had developed PJK. The risk of developing PJK between rib-based and spine-based growing systems was not significantly different at immediate post-operative follow-up (17% vs. 25%) or at final follow-up (25% vs. 31%). The primary purpose of the above-mentioned study was to compare the risk of developing PJK between rib and spine-based treatments. As a byproduct, high PI was found to increase the risk of developing PJK (risk ratio 3.1). Also, the radiographs of 362 children from the CSSG and the Growing Spine Study Group (GSSG) EOS registries with more than two years of follow up who were treated with distraction based implants were evaluated in a separate study.[97] The purpose was to compare the risk of clinically significant PJK between proximal rib vs. spine anchors. Sixty of 253 rib anchored and 31 of 109 spine anchored patients required proximal extension of the UIV for an overall risk of 25% (24% rib vs 28% spine, P=0.34).

The primary interest of this study is to evaluate the effect of spinopelvic morphology on the development of PJK in EOS patients treated with growth-friendly constructs. The research in this thesis proposal will add spinopelvic measurements and HRQOL to this data set in order to correlate relationships between pelvic morphology, HRQOL, and PJK. These correlations have not yet been researched.

2. Hypothesis

Non-physiological preoperative spinopelvic alignment (PI, PT, SS, PI-LL) in children with EOS increases the risk of developing PJK during the treatment with distraction-based growth friendly spine surgery.

3. Research Aims

3.1. General aim

To determine the effect of spinopelvic parameters on PJK development in EOS patients.

3.2. Specific aims

1) To determine the effect of pre-operative pelvic morphology on PJK in EOS patients treated with growth friendly surgery with minimum 2-year follow-up.

2) To determine the impact of post-operative spinopelvic alignment on PJK in EOS patients treated with growth-friendly surgery with minimum 2-year follow-up.

3) To determine the effect of spinopelvic alignment on HRQOL in EOS patients treated with growth friendly surgery with minimum 2-year follow-up.

4) To determine the rate of PJK (both radiographic and clinically significant) in EOS patients treated with growth friendly surgery with minimum 2-year follow-up

4. Materials and Methods

This was a retrospective cohort study of a group of children from two registries, the CSSG and the GSSG. Only children treated operatively with rib- or spine-based distraction implants for EOS between April 1997 and August 2012 were included. Data acquisition and analysis was performed by myself in the period from September 2014 to November 2017. Approval for use of the acquired data for the applicant's doctoral thesis was obtained on October 18th 2016 from leaders of both registries, the GSSG and the CSSG, respectively. Institutional review board approval from each site was obtained for each patient enrolled in the registries by the respective Institution, together with consent from the patients' caregivers for use of data in future research. This research was approved by the Research Ethics Committee of the Zagreb University School of Medicine on the 30th of January 2018.

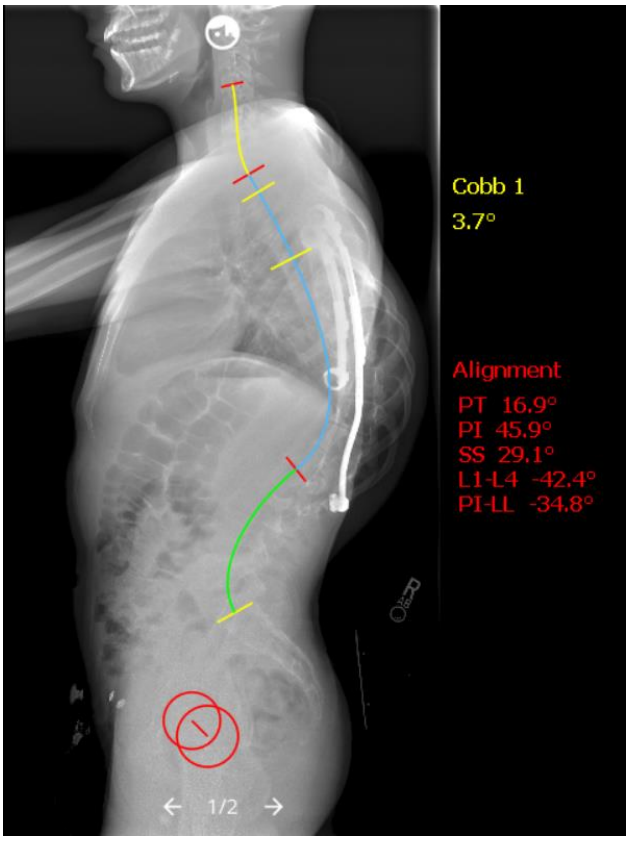
The inclusion criteria consisted of EOS patients aged younger than 10 years at time of diagnosis, treatment with distraction implants, and evaluation at most recent follow-up (mean 4.53 years ± 2.59). Excluded were patients older than 10 years at time of diagnosis, those treated with spine fusion surgery, or patients with missing radiographs.

Demographic data collected included age, etiology of EOS diagnosis, type of surgery, type of implant and time of follow-up. Preoperative and postoperative standing PA and lateral radiographs of the spine and pelvis were evaluated by a single observer (the applicant, O.K.). Spinal measurements were performed using the Surgimap software (Nemaris Inc., New York, USA) (Figure 10) and included: thoracic and lumbar CA, TK (high TK defined as >50°), LL (high LL defined as ≥70°), PT (high PT defined as >30°), SS, PI (high PI>60°), PI-LL (high PI-LL >20°) and proximal

junctional angle (PJA). Radiographic PJK was defined as sagittal PJA ≥ 10° and post-operative PJA at least 10° greater than preoperative measurement.[75,98] The requirement for proximal extension of the UIV during revision surgery was used as a surrogate for clinically significant PJK (clinical PJK).[97] This requirement was considered as failure of the proximal junction, dependent on surgeon preference. This structural failure could present itself as vertebral body fracture, implant pull-out or breakage, and/or disruption of the posterior ligament complex.

Figure 10. A graphic depiction of measurements using the Surgimap software (Nemaris Inc., New York, United States of America) on a randomly chosen patient from the Children's Spine Study Group registry. The sagittal plane radiograph is performed in a standing position. The software guides the user into choosing required elements of the patient's anatomy – femoral heads (two circles), sacral plateau (line on top of sacral plateau), upper endplate of the first lumbar vertebra (line on top of the first lumbar verterbra), upper endplate of the first thoracic vertebra (line on top of the first thoracic vertebra) and upper endplate of the second cervical vertebra (cervical spine measurements not used in the study, shown here for illustration purposes only). Once all the points are marked, the software measures and calculates all spinal and pelvic sagittal parameters automatically – thoracic kyphosis (TK), lumbar lordosis (L1-L4), pelvic incidence (PI), pelvic tilt (PT), sacral slope (SS), pelvic incidence lumbar lordosis mismatch (PI-LL). All the values are stated adjacent to the radiograph (Alignment).

Two lines in the upper thoracic spine show an additional measurement, that of the proximal junctional angle (PJA), according to Glattes et al.[75] The value of PJA is given in lettering, adjacent to the radiograph (Cobb 1 3.7°).



The HRQOL branch of the study was performed in a sub segment of patients who were evaluated with a HRQOL questionnaire made specifically for EOS patients and their caregivers, the Early Onset Scoliosis Questionnaire-24 (EOSQ-24 – Appendix 1, Instructions on scoring the EOSQ-24 – Appendix 2). The questionnaire had to be filled out by the caregiver prior to commencement of treatment and at final follow-up, so only those patients with questionnaires filled out at both time points were evaluated. This is a validated measurement tool for HRQOL in EOS patients, in use since year 2011.[99,100] The questionnaire has 24 items in 11 domains. For HRQOL domains: General health (2 items), Pain/Discomfort (2 items), Pulmonary function (2 items), Transfer (1 item), Physical Function (3 items), Daily Living (2 items), Fatigue/Energy level (2 items), Emotion (2 items), Parental burden (5 items), Financial

burden (1 item), Satisfaction (2 items) – scores ≥ 80 were considered good outcomes, while scores < 80 were considered to signify a poor outcome.

Appendix 1 – Early Onset Scoliosis 24-item Questionnaire (EOSQ-24)

General Health: <u>During the past 4 weeks</u>				
1. In general, you would say your child's health has been:				
Poor	Fair	Good	Very good	Excellent
2. How often has your child been sick?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time

Pain/Discomfort : <u>During the past 4 weeks</u>				
3. How often has your child had pain/discomfort?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
4. How severe has your child's pain/discomfort been?				
Very Severe	Severe	Moderate	Mild	No Pain

Pulmonary Function: <u>During the past 4 weeks</u>				
5. How difficult has it been for your child to cry/babble/speak (appropriate for age) without experiencing shortness of breath?				
Difficult	Somewhat Difficult	Neutral	Somewhat easy	Easy
6. How often has your child experienced shortness of breath during activities?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time

Transfer: <u>During the past 4 weeks</u>				
7. How often has your child's health condition limited his/her access to places?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time

Physical Function: During the past 4 weeks				
8. How difficult has it been for your child to move his/her upper body?				
Difficult	Somewhat difficult	Neutral	Somewhat easy	Easy
9. How difficult has it been for your child to sit up on his/her own?				
Difficult	Somewhat difficult	Neutral	Somewhat easy	Easy
10. How difficult has it been for your child to keep his/her balance while crawling, walking, or running?				
Difficult	Somewhat difficult	Neutral	Somewhat easy	Easy

Daily Living: During the past 4 weeks				
11. How difficult has it been for your child to dress him/herself or assist with dressing? **(examples: helping remove/ putting-on clothing, pushing arms and legs through shirts and pants, or assisting with fasteners, zippers, snaps, buttons, velcro)**				
Difficult	Somewhat difficult	Neutral	Somewhat easy	Easy
12. My child needs more time than a healthy child to eat the same amount of food.				
Strongly agree	Inclined to agree	Neither	Inclined to disagree	Strongly disagree

Fatigue/Energy Level: During the past 4 weeks				
13. How often has your child had fatigue?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
14. How difficult has it been for your child to keep up his/her energy all day?				
Difficult	Somewhat difficult	Neutral	Somewhat easy	Easy

Emotion: During the past 4 weeks
15. How often has your child felt anxious/ nervous due to his/her health condition?

All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
16. How often has your child felt frustrated due to his/her health condition?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time

Parental Impact: <u>During the past 4 weeks</u>				
17. How often have you felt anxious/nervous about his/her health condition?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
18. How often has your child's health condition interfered with family activities?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
19. How much has your child's health condition affected your energy level?				
Extremely	A lot	Some	A little	Not at all
20. How often have you missed or have you been late for work or social events due to your child's health condition?				
All of the time	Most of the time	Some of the time	A small amount of the time	None of the time
21. Have you been able to spend enough time with your family/partner/spouse despite your child's health condition?				
None of the time	A little of the time	Some of the time	Most of the time	All of the time

Financial Impact: <u>During the past 4 weeks</u>				
22. How much of a financial burden has your child's diagnosis of Early Onset Scoliosis been?				
Extreme burden	Quite a burden	Moderate burden	A little bit of a burden	No burden

Satisfaction: <u>During the past 4 weeks</u>				
23. How satisfied <u>is your child</u> with his/her ability to do things?				
Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied

24. How satisfied <u>are you</u> with your child's ability to do things?				
Very dissatisfied	Dissatisfied	Neutral	Satisfied	Very satisfied

Appendix 2 – Instructions on scoring the EOSQ-24

Scales and Items

Scale/Item Name (and Abbreviation)		Number of Items
Child's Health Related Quality of Life		16
	General Health (GH)	2
	Pain/Discomfort (PD)	2
	Pulmonary Function (PF)	2
	Transfer (TF)	1
	Physical Function (PH)	3
	Daily Living (DL)	2
	Fatigue/Energy Level (FE)	2
	Emotion (EM)	2
Family Impact		6
	Parental Impact (PI)	5
	Financial Impact (FI)	1
Satisfaction		2
	Child Satisfaction (CS)	1
	Parent Satisfaction (PS)	1
TOTAL		24

General Health (GH)		
Item	Response Choices	Item Values
1. In general, you would say your child's health has been:	Poor Fair Good Very good Excellent	1 2 3 4 5
2. How often has your child been sick?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm: (algebraic mean of the two items -1) *100		

4
3. Transformed scores should be 0 to 100

Pain/Discomfort (PD)		
Item	Response Choices	Item Values
3. How often has your child had pain/discomfort?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
4. How severe has your child's pain/discomfort been?	Very Severe Severe Moderate Mild No Pain	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm: (algebraic mean of the two items -1) *100 4		
3. Transformed scores should be 0 to 100		

Pulmonary Function (PF)		
Item	Response Choices	Item Values
5. How difficult has it been for your child to cry/babble/speak (appropriate for age) without experiencing shortness of breath?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
6. How often has your child experienced shortness of breath during activities?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm:		

(algebraic mean of the two items -1) / 4 *100
3. Transformed scores should be 0 to 100

Transfer (TF)		
Item	Response Choices	Item Values
7. How often has your child's health condition limited his/her access to places?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
Scale Scoring		
1. Create raw scores by recording the item value for those respondents who completed the one item; set missing those respondents who answered no items.		
2. Transform the value of the item choice to standardized 0 to 100 score using the following algorithm: (Value of Item Choice -1) / 4 *100		
3. Transformed scores should be 0 to 100		

Physical Function (PF)		
Item	Response Choices	Item Values
8. How difficult has it been for your child to move his/her upper body?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
9. How difficult has it been for your child to sit up on his/her own?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
10. How difficult has it been for your child to keep his/her balance while crawling, walking, or running?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of items answered for those respondents who completed two items or more; set missing for those respondents who answered one or no items.		
2. Transform the algebraic mean of the items answered to standardized 0 to 100 scores using the following algorithm: (algebraic mean of items answered -1) / 4 *100		
3. Transformed scores should be 0 to 100		

Daily Living (DL)		
Item	Response Choices	Item Values
11. How difficult has it been for your child to dress him/herself or assist with dressing?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
12. My child needs more time than a healthy child to eat the same amount of food.	Strongly Agree Inclined to agree Neither Inclined to disagree Strongly disagree	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm: $\frac{\text{(algebraic mean of the two items -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Fatigue/Energy Level (FE)		
Item	Response Choices	Item Values
13. How often has your child had fatigue?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
14. How difficult has it been for your child to keep up his/her energy all day?	Difficult Somewhat Difficult Neutral Somewhat easy Easy	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm: $\frac{\text{(algebraic mean of the two items -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Emotion (EM)		
Item	Response Choices	Item Values
15. How often has your child felt anxious/ nervous due to his/her health condition?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
16. How often has your child felt frustrated due to his/her health condition?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the two items for those respondents who completed one item or more; set missing for those respondents who answered no items.		
2. Transform the algebraic mean of the two items to standardized 0 to 100 scores using the following algorithm: $\frac{\text{(algebraic mean of the two items -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Parental Impact (PI)		
Item	Response Choices	Item Values
17. How often have you felt anxious/nervous about his/her health condition?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
18. How often has your child's health condition interfered with family activities?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5
19. How much has your child's health condition affected your energy level?	Extremely A lot Some A little Not at all	1 2 3 4 5
20. How often have you missed or have you been late for work or social events due to your child's health condition?	All of the time Most of the time Some of the time A small amount of the time None of the time	1 2 3 4 5

21. Have you been able to spend enough time with your family/partner/spouse despite your child's health condition?	None of the time A little of the time Some of the time Most of the time All of the time	1 2 3 4 5
Scale Scoring		
1. Create raw scores by computing the algebraic mean of the items answered for those respondents who completed three items or more; set missing for those respondents who answered one, two, or no items.		
2. Transform the algebraic mean of the items answered to standardized 0 to 100 scores using the following algorithm: $\frac{\text{(algebraic mean of items answered -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Financial Impact (FI)		
Item	Response Choices	Item Values
22. How much of a financial burden has your child's diagnosis of Early Onset Scoliosis been?	Extreme Burden Quite a burden Moderate burden A little bit of a burden No burden	1 2 3 4 5
Scale Scoring		
1. Create raw scores by recording the item value for those respondents who completed the one item; set missing for those respondents who answered no items.		
2. Transform the value of the item choice to standardized 0 to 100 score using the following algorithm: $\frac{\text{(Value of Item Choice -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Child Satisfaction (CS)		
Item	Response Choices	Item Values
23. How satisfied is your child with his/her ability to do things?	Very dissatisfied Dissatisfied Neutral Satisfied Very satisfied	1 2 3 4 5
Scale Scoring		
1. Create raw scores by recording the item value for those respondents who completed the one item; set missing for those respondents who answered no items.		
2. Transform the value of the item choice to standardized 0 to 100 score using the following algorithm: $\frac{\text{(Value of Item Choice -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

Parent Satisfaction (PS)		
Item	Response Choices	Item Values
24. How satisfied are you with your child's ability to do things?	Very dissatisfied Dissatisfied Neutral Satisfied Very satisfied	1 2 3 4 5
Scale Scoring		
1. Create raw scores by recording the item value for those respondents who completed the one item; set missing for those respondents who answered no items.		
2. Transform the value of the item choice to standardized 0 to 100 score using the following algorithm: $\frac{\text{(Value of Item Choice -1)}}{4} * 100$		
3. Transformed scores should be 0 to 100		

4.1. Statistical analysis

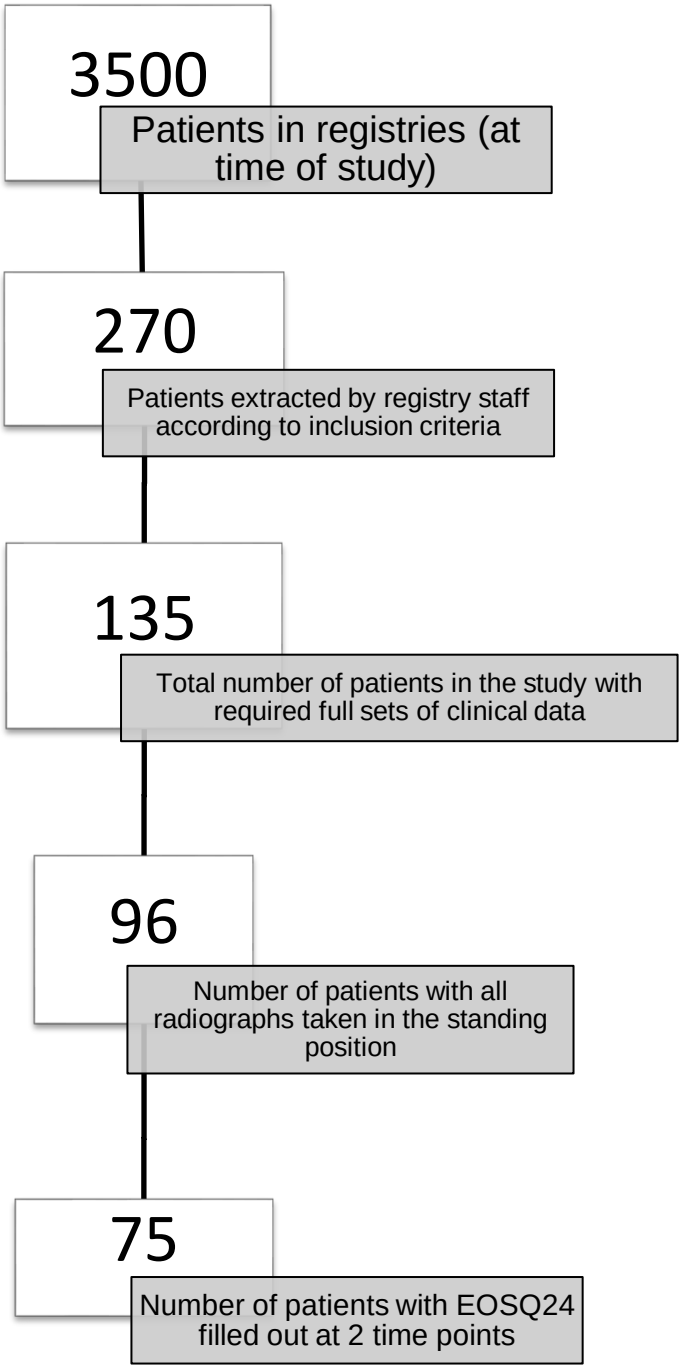
Statistical analysis was performed using (SPSS Version 24.0; Armonk IBM) and OpenEpi (OpenEpi 3.03; Atlanta, GA). Two-tailed t-test statistics or Wilcoxon rank sum tests were used to analyze continuous data, with a significance level of $P < 0.05$. Chi-square and Fisher exact tests were utilized to determine risk and risk ratio between different groups of patients. Because the a priori predictions were directional, one-tailed tests were used, with a significance level of $P < 0.05$.

5. Results

In total, among 2000 (CSSG) and 1500 (GSSG) patients included in the registries at the time of the study, 270 were chosen for this study by a respective registry staff member (T.St.H, J.P.) according to the following criteria – EOS patients treated operatively with growing instrumentation and minimum 2 year follow-up. After detailed review performed by myself, from the initially chosen 270, a total of 135 patients were deemed eligible for the study, 84 from the CSSG registry and 51 from the GSSG. This further selection was made by evaluating the data quality, all requested time points, as well as the technical aspects of their respective radiographs. As the registries include inputs from institutions hailing from multiple countries, there were inconsistencies in data acquisition and quality that caused the exclusion of 135 patients. Among the chosen patient cohort, 39 patients had all the necessary data and adequate follow-up, however their radiographs were taken in the seated position mainly due to their medical condition (or other reasons) prompting their elimination from the radiographic branch of the study, leaving 96 patients in the radiographic PJK branch (Figure 11).

Figure 11. A flowchart of the number of patients. At the time of study the registries had 3500 patients in total (natural history cases, non-surgical treatment and surgical treatment). Registry staff extracted 270 patients who were surgically treated with growth friendly instrumentation and minimum 2 years of follow-up. Out of the 270 patients, 135 were chosen by myself after detailed review of their clinical and radiographic data. Out of the 135, 96 had full radiographic workup performed in the standing position and were used for spinopelvic radiographic assessment. Out of the

96, 75 had a health related quality of life questionnaire filled at two time points by their



parents or caregiver and were included in the health quality assessment branch.

The total sample (N = 135) included 54 congenital scoliosis patients, 10 neuromuscular scoliosis patients, 37 patients with syndromic scoliosis, 32 idiopathic

scoliosis patients and two patients with unknown etiology, due to failure of the enrolling physician to record it in the system. Of the 135 children included, 119 (88%) were ambulatory, 2 (1.5%) were nonambulatory, 5 (3.7%) were preambulatory, while the ambulatory status for 9 patients was not available. The patients were treated at an average age of 5.3 ± 2.83 years (range, 0.97-12.18 years) with posterior distraction-based implants. Eighty-nine patients had rib-based (86 VEPTR, 3 GR with rib anchors) and 46 patients had spine-based distraction implants used, all GR with spine anchors. None had a MCGR implant. In the rib-based implant group, 55 patients (62%) had unilateral and 34 patients (38%) had bilateral instrumentation. In the spine-based implant group, one patient had a single rod and 45 patients had dual rod constructs.

Of the 135 patients in the study 96 of them (71.1%) had adequate quality radiographs taken in the standing position, which were deemed suitable for reliable measurements of spinopelvic parameters to be acquired, and these patients were included for the spinopelvic radiographic assessment (Table 1). The etiologies of scoliosis for these 96 patients were as follows; 39 congenital, 26 idiopathic, 24 syndromic, 6 neuromuscular and 1 unknown. Overall, 25 patients had one construct, 70 patients required two constructs and one patient had three constructs. Proximal anchor levels for the rib-based implant group ranged from T1-T9 and for the spine-based implant group from C7 to T5. Distal anchor levels ranged from T10 to pelvis for patients with rib-based implants and from T12 to pelvis for patients with spine-based implants. At final follow-up, patients had an average age of 9.9±3.42 years (range, 2.64 to 20.28 years), the minimum being two years of follow-up, averaging at 4.5 years ± 2.6, four patients with initial rib-based implants and six patients with initial spine based-implants had undergone final fusion (so called “graduates”).

The major curve decreased by 17% pre-operatively to most recent follow-up (71º vs. 56º, P<0.005, paired samples t-test) (Table 2). In addition, growth-friendly surgery affected spinopelvic parameters LL (52º pre-op. vs. 55º follow-up, P<0.029, Wilcoxon Signed Rank test) and PI (49º pre-op. vs. 52º follow-up, P<0.005, paired samples t-test), however, the PI-LL relationship remained unchanged (P=0.706, Wilcoxon Signed Rank test).

Table 1. Breakdown of patient number per assessment group. This table depicts the numbers of patients that exhibited no proximal junctional kyphosis (PJK), radiographic PJK or clinical PJK among the three main assessment groups.

Study branch	Clinical and radiological PJK assessment	Spinopelvic radiographic assessment	Health related quality of life assessment
Number of analyzed patients per assessment group	135	96	75
No PJK	75 (55%)	42 (44%)	42 (56%)
Radiographic PJK	36 (27%)	36 (38%)	20 (27%)
Clinical PJK	24 (18%)	18 (19%)	13 (19%)

Table 2. Scoliosis curve and sagittal parameters measurements of 135 patients included in the study: preoperative values and values at most recent follow-up

Parameters	**Pre-op**	**Most recent follow-up**	**P-Value**
Scoliosis Angle (º, mean±SD)	71.2±20.6 (range 14 to 128)	55.8±20.9 (range 2 to 98)	***<0.005****
Thoracic Kyphosis (º, mean±SD)	39.1±23.2 (range -5 to 115)	42.0±23.2 (range 1 to 112)	0.086ǂ
Lumbar Lordosis (º, mean±SD)	51.8±16.1 (range -8 to 97)	55.3±16.5 (range 16 to 98)	***0.029ǂ***
Pelvic Tilt (º, mean±SD)	10.8±10.9 (range -20 to 42)	13.1±12.7 (range -15 to 58)	0.100ǂ
Sacral Slope (º, mean±SD)	38.4±11.1 (range 12 to 84)	39.3±12.5 (range 9 to 80)	0.287ǂ
Pelvic Incidence (º, mean±SD)	48.9±12.4 (range 16 to 80)	52.1 ±14.2 (range 23 to 97)	***<0.005****
PI-LL (º, mean±SD)	-2.94±17.82 (range -49 to 73)	-3.19±18.76 (range -43 to 62)	0.706ǂ
* Paired samples t-test; ǂ Wilcoxon Signed Rank test LEGEND: SD – standard deviation, PI-LL – pelvic incidence lumbar lordosis mismatch			

Radiographic and clinical proximal junctional kyphosis development

Radiographic PJK developed in 38% of patients (36 of 96). The occurrence of radiographic PJK was higher in syndromic (54%) and neuromuscular (50%) EOS patients compared to idiopathic (38%) and congenital (23%) EOS patients, but this difference did not reach statistical significance (P=0.063, Wilcoxon Signed Rank test).

Twenty-four of 135 patients (18%) required a proximal extension of the UIV during revision surgery, here defined as clinical PJK. The occurrence of clinical PJK was not statistically significant different between etiologies (135 patients, P=0.230, Wilcoxon Signed Rank test); 24% of syndromic, 30% of neuromuscular, 16% of idiopathic and 11% of congenital EOS patients had clinical PJK.

Patients treated with rib-based constructs had a lower risk to develop radiographic PJK compared to spine-based constructs (96 patients, PJK: 31% rib vs. 54% spine; RR: 0.584, 95%CI: 0.355-0.959; P=0.044, paired sample t-test). However, construct type did not affect risk of developing clinical PJK (135 patients, RR: 0.861, 95%CI: 0.409, 1.816; P=0.696, paired sample t-test).

Sagittal parameters as risk factors for proximal junctional kyphosis

To identify radiographic risk factors for developing both clinical and radiographic PJK, Chi square analysis or Fisher's exact test were used. Of all pre-operative spinopelvic parameters analyzed, only pre-operative TK >50^{o} increased the risk for developing radiographic PJK (RR: 1.667, 95%CI: 0.981-2.832; P=0.04, Wilcoxon Signed Rank test; Table 3). For clinical PJK, none of the pre-operative spinopelvic parameters was found to be a risk factor (Table 3).

Table 3. Relative risk of radiographic (for 96 patients with full radiographic workup performed in the standing position) and clinical (for 135 patients with full clinical data sets) proximal junctional kyphosis related to pre-operative spinopelvic parameters

Pre-operative Spinopelvic Parameters	**PJK**	**Relative Risk**	***95% Confidence Interval***	***P-value***
Thoracic Kyphosis >50º	Radiographic PJK	1.667	0.981-2.832	***0.04***
Lumbar Lordosis >70º	Radiographic PJK	0.966	0.422-2.211	0.605
Pelvic Tilt >30º	Radiographic PJK	0.657	0.118-3.660	0.518
Pelvic Incidence >60º	Radiographic PJK	1.029	0.715-1.482	0.440
PI-LL >20º	Radiographic PJK	0.782	0.292-2.091	0.883
Thoracic Kyphosis >50º	Clinical PJK	0.952	0.411-2.206	0.455
Lumbar Lordosis >70º	Clinical PJK	0.727	0.190-2.789	0.317
Pelvic Tilt >30º	Clinical PJK	N/A		0.301
Pelvic Incidence >60º	Clinical PJK	0.522	0.167-1.629	0.183
PI-LL >20º	Clinical PJK	1.025	0.277-3.796	>0.999

LEGEND: PJK – proximal junctional kyphosis, PI-LL – pelvic incidence lumbar lordosis mismatch

Analysis of the post-operative spinopelvic parameters revealed that none of these were risk factors for developing radiographic PJK (Table 4). However, a post-operative PT >30° (RR: 2.47, 95%CI: 1.107-5.508; P=0.02, Wilcoxon Signed Rank test) and PI-LL >20º (RR: 2.105, 95%CI: 0.922-4.809; P=0.047, Wilcoxon Signed Rank test) increased the risk of developing clinical PJK (Table 4).

Table 4. Relative risk of radiographic (for 96 patients with full radiographic workup performed in the standing position) and clinical (for 135 patients with full clinical data sets) proximal junctional kyphosis according to post-operative spinopelvic parameters

Post-operative Spinopelvic Parameters	**PJK**	**Relative Risk**	**95% Confidence Interval**	***P-value***
Pelvic Tilt >30º	Radiographic PJK	1.545	0.839-2.848	0.107
PI-LL >20º	Radiographic PJK	1.545	0.839-2.848	0.107
Thoracic Kyphosis >50º	Radiographic PJK	0.889	0.495-1.595	0.688
Lumbar Lordosis >70º	Radiographic PJK	0.581	0.237-1.425	0.190
Pelvic Incidence >60º	Radiographic PJK	1.243	0.735-2.103	0.426
Pelvic Tilt >30º	Clinical PJK	2.47	1.107-5.508	***0.020***
PI-LL >20°	Clinical PJK	2.105	0.922-4.809	***0.047***
Thoracic Kyphosis >50º	Clinical PJK	0.852	0.381-1.901	0.693
Thoracic Kyphosis >40º	Clinical PJK	0.967	0.467-2.003	0.928
Lumbar Lordosis >70º	Clinical PJK	1.158	0.478-2.803	0.748
Pelvic Incidence >60º	Clinical PJK	1.146	0.533-2.464	0.729

LEGEND: PJK – proximal junctional kyphosis, PI-LL – pelvic incidence lumbar lordosis mismatch

Proximal junctional kyphosis versus “No” proximal junctional kyphosis

Comparisons of patients with radiographic (96 patients) or clinical (135 patients) PJK to patients who did not develop PJK, comprising the so-called “No PJK” group, revealed no differences in pre- and post-operative sagittal alignment among the

groups (Tables 5 and 6). The major curve was larger in the clinical PJK group compared to “No PJK” at most recent follow-up, however the magnitude of curve correction was similar (Table 5). Although none of the radiographic parameters was statistically significant different between groups pre-operatively or at most recent follow-up, the magnitude of change for PT and PI from pre-operative to most recent follow-up was greater in the clinical PJK group compared to No PJK ($P<0.05$, paired samples t-test) for each comparison), and there was a tendency to a greater change of PI-LL in the clinical PJK group as well ($P=0.062$, Wilcoxon Signed Rank test) (Tables 5 and 6).

Table 5. Comparison of spinal and spinopelvic measurements in “Clinical proximal junctional kyphosis” group versus the “No clinical proximal junctional kyphosis” group

Parameters	**No clin. PJK**	**Clin PJK**	***P-value***
Age at surgery (years, mean±SD)	5.1±2.9	6.1±2.3	*0.102*
PJA post-operative (°, mean±SD)	6.1±8.7	9.6±8.0	*0.104*
Levels fused post-op (#, mean±SD)	13.1±2.5	13.2±2.6	*0.911*
Major Curve			
pre-operative (°, mean±SD)	70.5±20.4	76.4±21.2	*0.177*
last follow-up (°, mean±SD)	53.6±21.4	65.1±15.9	***0.015***
Δ pre-operative - last follow-up (%)	18 ±45	12 ± 22	*0.495*
Thoracic Kyphosis			
pre-operative (°, mean±SD)	38.8±23.4	40.7±22.6	*0.687*
last follow-up (°, mean±SD)	42.3±23.3	40.4±23.4	*0.756*
Δ pre-operative - last follow-up (°, mean±SD)	3.5±23.3	-0.3 ±17.8	*0.360*
Lumbar Lordosis			

pre-operative (°, mean±SD)	51.7±16.3	52.2±15.5	*0.886*
last follow-up (°, mean±SD)	55.7±15.4	53.1±21.1	*0.475*
Δ pre-operative - last follow-up (°, mean±SD)	4.0±17.9	0.9 ±23.4	*0.700*
Pelvic Tilt			
pre-operative (°, mean±SD)	11.4±11.0	8.3±9.9	*0.215*
last follow-up (°, mean±SD)	12.4±11.2	16.7±18.1	*0.430*
Δ pre-operative - last follow-up (°, mean±SD)	0.99±10.5	8.3 ±16.8	***0.049***
Pelvic Incidence			
pre-operative (°, mean±SD)	49.5±12.3	46.0±12.8	*0.216*
last follow-up (°, mean±SD)	51.4±14.0	55.4±14.9	*0.212*
Δ pre-operative - last follow-up (°, mean±SD)	1.9±8.9	9.4 ±10.8	***0.002***
Sacral Slope			
pre-operative (°, mean±SD)	38.6±10.5	38.0±14.0	*0.861*
last follow-up (°, mean±SD)	39.3±12.3	39.0±14.1	*0.915*
Δ pre-operative - last follow-up (°, mean±SD)	0.77±10.5	1.08±15.6	*0.927*
PI-LL			
pre-operative (°, mean±SD)	-2.2±18.0	-6.2±17.0	*0.251*
last follow-up (°, mean±SD)	-4.4±16.4	2.3±27.0	*0.254*
Δ pre-operative - last follow-up (°, mean±SD)	-2.1 ± 18.7	8.5 ±25.4	***0.062***
LEGEND: PJA – proximal junctional angle, PJK – proximal junctional kyphosis, PI-LL – pelvic incidence lumbar lordosis mismatch, SD – standard deviation			

Table 6. Comparison of spinal and spinopelvic measurements in the “radiographic proximal junctional kyphosis” group versus the “No radiographic proximal junctional kyphosis” group

Spinopelvic Parameters	**No radiographic PJK**	**Radiographic PJK**	***P-value***
Age at surgery (years, mean±SD)	5.0±2.9	5.4±2.9	*0.507*
PJA post-op (°, mean±SD)	1.7±5.6	15.4±5.3	***<0.005***
Levels fused post-op (#, mean±SD)	13.3±2.3	12.9±2.7	*0.504*
Cobb Angle			
pre-operative (°, mean±SD)	73.2±19.3	66.2±22.1	*0.110*
last follow-up (°, mean±SD)	58.8±20.2	53.6±20.8	*0.134*
Change pre-operative to last follow-up (%)	15 ± 34	9 ± 64	*0.560*
Thoracic Kyphosis			
pre-operative (°, mean±SD)	34.1±21.9	41.0±22.6	*0.114*
last follow-up (°, mean±SD)	41.3±23.1	42.6±24.4	*0.895*
Δ pre-operative - last follow-up (°, mean±SD)	7.2 ± 19.6	1.55 ±19.1	*0.172*
Lumbar Lordosis			
pre-operative (°, mean±SD)	50.8±18.5	51.0±14.0	*0.853*
last follow-up (°, mean±SD)	54.5±17.9	54.0±16.8	*0.674*
Δ pre-operative - last follow-up (°, mean±SD)	3.7 ± 22.7	3.0 ±16.1	*0.866*
Pelvic Tilt			
pre-operative (°, mean±SD)	10.2±11.4	11.2±10.2	*0.664*
last follow-up (°, mean±SD)	11.5±12.0	15.3±16.4	*0.537*
Δ pre-operative - last follow-up (°, mean±SD)	1.3 ± 11.2	4.1 ±14.6	*0.305*
Pelvic Incidence			

pre-operative (°, mean±SD)	48.3±13.3	48.9±12.4	*0.814*
last follow-up (°, mean±SD)	50.1±14.3	53.5±16.6	*0.295*
Δ pre-operative - last follow-up (°, mean±SD)	1.8 ± 9.3	4.6 ±11.8	*0.627*
Sacral Slope			
pre-operative (°, mean±SD)	38.7±12.0	38.1±11.9	*0.655*
last follow-up (°, mean±SD)	38.9±13.3	38.5±13.1	*0.886*
Δ pre-operative - last follow-up (°, mean±SD)	0.2 ± 11.9	0.4 ±12.3	*0.525*
PI-LL			
pre-operative (°, mean±SD)	-2.5±21.0	-2.1±14.6	*0.759*
last follow-up (°, mean±SD)	-4.4±18.1	-0.4±23.0	*0.797*
Δ pre-operative - last follow-up (°, mean±SD)	-1.9 ± 21.3	1.6 ±2.1	*0.440*
LEGEND: PJA – proximal junctional angle, PJK – proximal junctional kyphosis, PI-LL – pelvic incidence lumbar lordosis mismatch, SD – standard deviation			

Health Related Quality of Life

Seventy-five children (out of the 96 with adequate radiographic workup) from two EOS registries, treated with rib (52) and spine (23) based distraction implants at a mean age of 5.4 years were evaluated with the EOSQ-24 and radiographs prior to treatment and at a mean follow-up of 4.5 years. Scores were compared using unpaired t-test, risk ratios were calculated and analysed using chi squared testing (Table 7).

Table 7. Results of the Early Onset Scoliosis Questionnaire-24 for 75 patients whose parents or caregivers filled out the form prior to the initial treatment and at final follow-up

EOSQ-24 Categories	**Score (0-100) Mean ± SD**	**Single Questions**	**Score (1-5) Mean ± SD**
General Health	78.6 ± 13.8	**General Health**	3.8 ± 1.0
		Illness Frequency	4.1 ± 0.7
Pain Discomfort	73.3 ± 19.2	**Pain Frequency**	3.5 ± 1.1
		Pain Severity	3.9 ± 0.9
Pulmonary	86.8 ± 16.7	**Pulmonary Difficulty**	4.5 ± 0.9
		Pulmonary Frequency	4.2 ± 1.0
Transfer	87.7 ± 17.8	**Transfer**	4.4 ± 0.9
Physical Function	87.3 ± 15.2	**Upper Body Movement**	4.1 ± 1.1
		Sitting Difficulty	4.6 ± 0.8
		Balance Difficulty	4.4 ± 1.0
Daily Living	79.5 ± 24.1	**Dressing Difficulty**	4.2 ± 1.2
		Time Eating	3.7 ± 1.6
Fatigue	83.1 ± 17.7	**Fatigue**	4.3 ± 0.8
		Energy	4.1 ± 1.1
Emotion	80.8 ± 16.3	**Child Anxiousness**	4.1 ± 0.9
		Frustration	3.9 ± 0.9
Parental Impact	80.4 ± 16.2	**Parent Anxiousness**	3.4 ± 1.1
		Family Activity	4.0 ± 1.0
		Parent Energy	4.0 ± 1.1

		Work Social	4.3 ± 0.9
		Family Impact	4.3 ± 1.0
Financial Burden	73.1 ± 26.3	**Financial Burden**	3.7 ± 1.2
Satisfaction	77.6 ± 20.0	**Child Satisfaction**	3.9 ± 1.0
		Parent Satisfaction	3.9 ± 1.1
LEGEND: EOSQ-24 – early onset scoliosis questionnaire 24, SD – standard deviation			

Etiologies included 32 congenital, 20 idiopathic, 18 syndromic, four neuromuscular, and one unknown. Pre-operatively, the major scoliotis curve was 69˚, TK 40˚, LL 51°, PI 48˚, and PT 11˚. At final follow-up, the major curve corrected to 55˚, TK was 42˚, LL 53˚, PI 53˚ and PT 15˚. Etiology affected General Health (P=0.007, Wilcoxon Signed Rank test) as outcomes were poor in 56% of syndromic and 50% of neuromuscular patients as compared to 25% of idiopathic and 9% of congenital patients.

A post-operative PI-LL mismatch of > ±20^{o} increased the risk for poor outcomes (score <80) in the following HRQOL domains: Fatigue (RR: 2.29, CI: 1.23-4.24, P=0.01, Wilcoxon Signed Rank test), Pain (RR: 1.70, CI: 1.07-2.71, P=0.04, Wilcoxon Signed Rank test), Daily Living (RR: 2.37, CI: 1.17-4.82, P=0.02, Wilcoxon Signed Rank test), Parental Impact (RR: 1.94, CI: 1.14-3.31, P=0.002, Wilcoxon Signed Rank test) and Emotion (RR: 1.82, CI: 1.03-3.22, P=0.05, Wilcoxon Signed Rank test). Post-operative LL > 70˚ increased the risk for high Family Burden (RR: 1.88, CI: 1.17-2.87, P=0.05, Wilcoxon Signed Rank test) and post-operative PI > 60˚ negatively impacted Transfer (RR: 1.76, CI: 1.24-13.25, P=0.008, Wilcoxon Signed Rank test). In contrast, pre- and post-operative TK > 40˚ decreased the risk for low Pulmonary Function (pre-op: RR: 0.202, CI: 0.05- 0.84, P=0.009, Wilcoxon Signed Rank test; post-op RR:

0.313, CI: 0.10- 1.03, P=0.018, Wilcoxon Signed Rank test). HRQOL was not affected by PT > 30˚, implant type or fusion to pelvis (Tables 8 and 9).

Table 8. The influence of spinopelvic parameters on the quality of life according to the results of the Early Onset Scoliosis Questionnaire-24

SP parameters	**Satisfaction <80**	**Satisfaction ≥80**	**Risk Ratio**	**95% CI**	**P - value**
LL > 60 pre-op	10	10	1.786	0.9566, 3.333	0.04
LL ≤ 60 pre-op	14	36			
LL > 60 post-op	11	9	2.115	1.146, 3.905	0.01
LL ≤ 60 post-op	13	37			
	Pain <80	**Pain ≥80**	**Risk Ratio**	**95% CI**	**P - value**
PI > 60 pre-op	9	3	1.76	1.136, 2.726	0.02
PI ≤ 60 post-op	26	35			
	Fatigue <80	**Fatigue ≥80**	**Risk Ratio**	**95% CI**	**P - value**
PI-LL > ±20 post-op	9	11	2.75	1.274, 5.935	0.014
PI-LL ≤ ±20 post-op	9	46			
LEGEND: SP – spinopelvic parameters, CI – confidence interval, LL – lumbar lordosis, PI – pelvic incidence, PI-LL – pelvic incidence lumbar lordosis mismatch					

Table 9. The influence of proximal junctional kyphosis on the quality of life according to the results of the Early Onset Scoliosis Questionnaire-24

	Radiographic PJK (20)	**No Radiographic PJK (35)**	**P-Value**	**Clinical PJK (13)**	**No Clinical PJK (62)**	**P-Value**
Age at surgery (yrs)	5.7 ± 2.9	4.8 ± 3.0	0.295	5.1 ± 3.7	5.4 ± 3.0	0.763
Follow-up questionnaire (yrs)	4.5 ± 3.5	4.3 ± 2.9	0.796	4.2 ± 3.0	4.3 ± 3.3	0.895

Follow-up Radiographs (yrs)	4.9 ± 3.1	4.8 ± 2.2	0.840	5.1 ± 2.7	4.4 ± 2.5	0.343
EOSQ Categories						
General	73.5 ± 15.0	80.0 ± 12.1	0.086	81.5 ± 9.0	78.0 ± 14.6	0.405
Pain/Discomfort	75.0 ± 19.1	73.2 ± 20.6	0.756	76.9 ± 18.0	72.5 ± 19.5	0.454
Pulmonary	84.0 ± 13.5	87.9 ± 14.1	0.329	90.8 ± 12.6	85.9 ± 17.4	0.348
Transfer	86.0 ± 17.3	87.6 ± 17.1	0.735	95.4 ± 8.8	86.0 ± 18.9	0.009
Physical	88.0 ± 15.2	88.2 ± 13.8	0.965	90.8 ± 12.6	86.6 ± 15.7	0.374
Daily living	75.0 ± 27.8	81.8 ± 22.4	0.332	87.7 ± 20.5	77.7 ± 24.6	0.177
Fatigue	76.5 ± 16.9	86.9 ± 14.7	0.021	88.5 ± 16.8	82.0 ± 17.8	0.231
Emotion	83.0 ± 15.3	80.6 ± 15.6	0.582	83.3 ± 17.8	80.3 ± 16.0	0.563
Parental impact	79.5 ± 13.8	80.3 ± 13.6	0.821	85.4 ± 15.1	79.4 ± 16.3	0.241
Finance	86.0 ± 23.5	68.5 ± 24.0	0.012	73.3 ± 27.4	73.0 ± 26.3	0.968
Satisfaction	80.0 ± 20.0	75.0 ± 19.9	0.385	88.2 ± 19.9	75.6 ± 19.5	0.054
LEGEND: PJK – proximal junctional kyphosis, EOSQ – early onset scoliosis questionnaire						

6. Discussion

The hypothesis stating abnormal preoperative spinopelvic anatomy will influence the occurrence of PJK, was not corroborated. In fact, the sole measurable preoperative parameter that had any significant impact on the arisal of radiographic PJK was TK>50°. However, when assessed postoperatively, patients with a PI-LL >20º and PT ≥30º were found to have 2.5 and 2.1 times higher risk of developing clinical PJK, respectively. These findings provide important information to the surgeon, who can now use methods discussed further in the text to try and avoid PJK in patients with a higher preoperative risk as well as avoid under- or overcorrecting the lumbar spine in the sagittal plane to negatively influence the spinopelvic anatomy.

The primary purpose of this doctoral thesis was to determine the effect of spinopelvic parameters on the development of PJK, be it radiographic or with clinical repercussions, in EOS patients treated with growing instrumentation. Clinical PJK, meaning failure of the proximal junction due to fracture, issues with hardware or myelopathy, was used in addition to radiographic PJK due to the intraobserver and interobserver variance associated with radiographic PJK measurements.[98,101] The decision on whether to act in a setting of a clinically significant PJK (i.e. pain, neurological symptoms) was dependant on the treating surgeon. In this cohort of 135 EOS patients surgically treated with growth friendly constructs, 18% developed clinical PJK. In the subgroup of 96 patients 38% developed radiographic PJK. A pre-operative TK >50° and the use of spine-based distraction constructs increased the risk for the development of post-operative radiographic PJK. Post-operative PT >30° and post-operative PI-LL >20° increased the risk for development of clinical PJK. In addition, patients with clinical PJK had greater changes in PT and PI at final follow-up.

Only a few studies have documented the effect of spinopelvic parameters on the development of postoperative PJK in EOS patients[82,83,84]. Given that EOS is an uncommon disease, this study of 135 patients is considered a large cohort when compared to other similar studies with the number of patients ranging from 14 to 68.[82,83,84] Data were collected from two multicenter study groups, which makes the results highly applicable to surgeons performing growth friendly surgery. This patient cohort included multiple etiologies, congenital (54), neuromuscular (10), syndromic (37), and idiopathic (32) and two patients with unknown etiology. Detailed subanalysis by etiology was not possible due to small sample size per etiology. Of note, etiology had no statistically significant effect on either radiographic or clinical PJK.

Previously reported risk factors for PJK in EOS include older age at index surgery, pre-operative thoracic hyperkyphosis, post-operative cervical hyperlordosis, postoperative segmental hyperkyphosis and PJA, high PI, screw or anchor malposition on the UIV, weak paraspinal muscular support, or hemivertebra.[83,102-104] In this patient cohort, preoperative TK >50° increased the risk for postoperative radiographic PJK. Thoracic hyperkyphosis has been consistently reported as a risk factor for PJK in EOS and AIS.[103,105-107] It was suggested that surgical correction of hyperkyphosis in order to achieve a physiological sagittal profile might induce imbalance of the spine, for which the trunk compensates by developing PJK.[108,109] Although in this cohort more hyperkyphotic EOS patients had radiographic PJK, it did not lead to a higher risk for re-operation with extension of the UIV.

The importance of pelvic orientation on thoracolumbar spine alignment and its implications on spine surgery has become increasingly evident in the adult spine literature.[110-112] Pelvic alignment is most commonly assessed using PT, which reflects compensatory pelvic retroversion for spinal deformity, and PI, which determines LL,

as well as SS. During growth, PI and PT tend to increase, while SS remains stable.[73] In adjacent segment disease (ASD) patients, a postoperative PT<20° or a postoperative PI-LL between 10° and 20° was associated with a lower incidence of PJK.[112,113] In a previous study of 40 EOS patients, pre-operative PT tended to be higher in PJK patients compared to those without PJK, but did not reach statistical significance.[103] Although we did not observe any effect of pre-operative PT on development of PJK, a post-operative PT ≥30° was a risk factor for clinical PJK (P=0.04, paired samples t-test). In addition, we found that a post-operative PI-LL>20° was associated with increased risk for clinical PJK. Comparisons between PJK and "No PJK" patients showed that the magnitude of change for PT and PI was higher in clinical PJK patients. This suggests that patients who developed clinical PJK underwent significantly greater changes in alignment. Pelvic parameters should therefore be taken into account when planning surgical correction to decrease the occurrence of PJK.

Distraction-based implants are used to correct spinal deformities in EOS patients by mechanically applying a distractive force across the deformed segment of the spine with anchors at the top and bottom of the implants, which attach to the spine, rib or pelvis depending on patient characteristics of the curve, age and available bone stock.[52,53,114] There has been increasing interest in the effects of the different construct types, rib-based compared to spine-based surgery, on the occurrence of PJK. It was hypothesized that rib-based constructs might decrease the risk for developing PJK in comparison with the spine-based construct, given that they less likely disrupt the posterior ligamentous complex at the UIV. In addition, pedicle screws or hooks of spine-based constructs may increase load/compression forces on the proximal junction of the spine. The use of rib anchors rather than pedicle screws avoids fusion

at the proximal anchor site, allowing some motion of the implant construct, and resulting in lower PJA and flexion of proximal forces. A previous study of 40 EOS patients and a study by Chen et al. including 33 EOS patients found that, although not statistically significant, the incidence of PJK was slightly lower in patients treated with rib-based distraction as compared to spine-based distraction.[103,115] This study of 135 patients found a lower risk for radiographic PJK in patients with rib-based (31%) constructs compared to spine-based distraction constructs (54%). This suggests that using a more rigid system leads to a higher incidence of PJK.

The clinical relevance of an increase in proximal kyphosis has also been questioned. Although in this cohort 18% of EOS patients required revision of the UIV, other studies reported a low incidence of 0-6% for PJK requiring proximal surgical extension in EOS patients.[52,104,116] In addition, PJK can be corrected by extending the fusion during planned lengthening or at the final fusion surgery in EOS patients undergoing growth-friendly surgery. Although the impact of PJK on the overall treatment plan might therefore be minimal, revisions add risks of perioperative complications to the patient. Adjustment of surgical correction goals and thoracic compensation will help to reduce the risk for development of PJK in young children with scoliosis.

Assessing quality of life in patients with EOS is a difficult task, due to evident heterogeneity of the targeted population in aspects such as etiology, patient age, comorbidities. Standard adult health measures cannot be used to assess the pediatric population. Thus, the EOSQ-24 was developed and validated for this subgroup of scoliosis patients.[99] The results of the evaluation of HRQOL revealed important considerations to be included in the preoperative discussions. Patients with a syndromic or neuromuscular scoliosis tend to have poorer quality of life scores in

general, with poor outcomes seen in 56% and 50%, respectively. As opposed to those children, patients undergoing the same types of treatment but with idiopathic and congenital etiology to their scoliosis exhibited poor results at a much lower rate (25% of idiopathic and 9% of congenital patients). This information can help set the family's expectation bar from the beginning of treatment as well as improve cooperation.

In this cohort of patients with EOSQ-24 results we have identifed three findings that significantly influence quality of life in these children. The first one is the PI-LL mismatch of > ±20° that negatively affected the Fatigue and Pain domains and also had a negative impact on the Emotion, Daily living and Parental domains. This fact is well known from the literature on adult spine patients, as a PI-LL mismatch of >10° is associated with adverse patient-reported outcomes.[117,118] Diebo et al. reported that increasing PI-LL mismatch caused the body to compensate by increasing pelvic retroversion, decreasing TK, and increasing both knee flexion and pelvic shift. In their paper the authors also demonstrated that the compensation mechanisms of the body for positive sagittal imbalance through PT and TK become depleted after 20° and 30° of PI-LL mismatch, respectively.[119] Continuous PI-LL mismatch together with overcompensation through PT and TK can cause PJK, adjacent segment pathology as well as pseudarthrosis.[111,113,120] The other two findings impacting HRQOL significantly were post-operative LL>70° and post-operative PI > 60°.

According to the relevant literature, the quality of life in patients with EOS is significantly impaired, especially regarding physical function and caregiver burden. These patients score lower on HRQOL questionnaires than those afflicted with cancer, heart disease, epilepsy or asthma.[99,121,122] EOS affects young children at a developmentaly extremely turbulent and formative time and the offered treatments purport multiple visits to the hospital and bear a high complication rate. All of this has

been shown to affect the children's psychosocial functioning to a significant extent. The effects of repetitive anesthesia on the developing brain have been reported to negatively affect both behavior and cognition.[123-125] In their report on the psychosocial impact of surgical treatment in EOS patients, both Matsumoto et al. and Flynn et al. found a higher prevalence of anomalous scores in numerous domains. Further, the authors reported that younger age at index surgery and a higher total number of surgeries performed correlated strongly with those abberant results.[126,127] However, Matsumoto et al. also reported on a noticeable increase in prosocial behavior correlated to an increased number of surgeries, demonstrating that the challenges these children face also help them become more resilient, mature faster than their healthy peers through developing strong coping mechanisms. Also, it was noted that the higher levels of anxiety and depression in these patients tend to decrease during the course of treatment, presumably because of the patients' maturation and understanding that their treatment is working in their favor.[126]

This study has several important weaknesses: its non-consecutive, retrospective nature, length of follow-up which does not include full maturity and the possible biases associated with its design. Because EOS is so rare, it is difficult to acquire large numbers of patients to study without examining a multi-center database. Thus, the study was performed by using two multicenter study groups as single center studies would lack of statistical power and could not reveal significant outcomes. Technical inconsistencies in radiograph acquisition quality among different institutions caused a great deal of patients with otherwise good quality data to be excluded from the study. Also, even in good quality radiographs, acquiring accurate measurements of all stated parameters proved a difficult task in the setting of scoliosis, especially at the upper end of the construct due to difficulties with discerning the most proximal

thoracic vertebrae. The multicentricity in question also brought about the unavoidable difference of opinions and, ultimately, types of treatment among institutions as well as individual surgeons. The registries in question also did not take into account gender, a simple demographic characteristic that could help shed light on a possible difference of risks for males versus females, or vice versa. Furthermore, the definition of PJK has been variable in the literature and its risk in the EOS population has been recently documented, varying from seven percent to 56% in the literature depending upon the definition used.[75,102] Therefore, clinical PJK was analyzed in addition to radiographic PJK, to account for difficulties in radiographic measurements due to the small stature of EOS patients, poor bone quality and variability in positioning for radiographs at different institutions. An additional important limitation to adress is the heterogeneity of etiologies and medical complexity of children with EOS included in the study. Taking into consideration the rarity of the disease itself, drawing conclusions only for a certain etiology would provide low power results from which sensible conclusions could not be drawn.

7. Conclusion

For patients with EOS undergoing growth-friendly surgery, preoperative TK >50º and spine-based distraction construct increase the risk of developing radiographic PJK; and postoperative PI-LL >20º and PT ≥30º increase the risk for clinical PJK. This stresses the importance of taking into account the spinopelvic parameters in pre-operative planning, given that the surgeon's ability to affect LL can influence these measurements. Furthermore, it prompts clinicians to take into account that the type of construct can also increase the development of PJK.

The HRQOL branch of the study showed that a postoperative PI-LL mismatch of > ±20 increases fatigue in patients, something also noted in patients who had exhibited radiographic PJK. Both pre- and postoperative LL >60° decreased the satisfaction category significantly. Preoperative PI >60° was shown to increase pain in everyday lives of patients. The etiology of scoliosis was found to have significant impact on general health, with 67% of syndromic scoliosis and 50% of neuromuscular scoliosis patients scoring poorly (<80).

8. Abstract in Croatian

Pre- i postoperativna spinopelvina anatomija utječu na rezultate liječenja djece s ranopojavnom skoliozom. Hipoteza predmnijeva da bolesnici s abnormalnom spinopelvinom anatomijom imaju veći rizik od nastanka kifoze proksimalnog spoja (KPS) u tijeku liječenja rastućim instrumentacijama. Ova studija obuhvatila je bolesnike liječene od travnja 1997. do kolovoza 2014. Kod dijela bolesnika evaluirana je i kvaliteta života. 135 bolesnika liječeno je u prosječnoj dobi od 5,3 ± 2,83 godina (raspon, 0,97-12,18) s minimalnim praćenjem od 2 godine (prosjek, 4,5 ± 2,6 godina). 96 bolesnika uključeno je u ispitivanje radiografske kifoze. Ukupno je upotrijebljeno 89 kralježničnih i 46 rebrenih instrumentacija. Radiografska KPS pronađena je u 38% (36/96), dok je ona klinički značajna otkrivena u 18% (24/135) bolesnika. Preoperativna torakalna kifoza (TK) >50° povećala je rizik za radiografsku KPS (RR: 1.667, P=0.04), dok preoperativni spinopelvini parametri nisu utjecali na razvoj klinički značajne kifoze. Utjecaj navedenih anatomskih varijanti na kvalitetu života bio je slijedeći: razlika incidence zdjelice i lordoze (eng. pelvic incidence lumbar lordosis mismatch (PI-LL)) >20° uzrokuje loš rezultat u multiplim domenama, nagib zdjelice (eng. pelvic tilt (PT)) >30°. Preoperativna TK >50° i kralježnične instrumentacije povećavaju rizik pojave radiografske kifoze, a postoperativni PI-LL >20° i PT ≥30º povećavaju rizik od klinički značajne kifoze. Preoperativna PI >60° uzrokuje bolove.

9. Abstract in English

Pre- and postoperative spinopelvic anatomy can influence results of distraction treatment in early onset scoliosis. I hypothesize patients with abnormal spinopelvic alignment have increased risk of proximal junctional kyphosis (PJK) during distraction treatment. Patients were treated between April 1997 and August 2014. A subsegment of patients were evaluated for quality of life. 135 patients were treated at an average age of 5.3 ± 2.83 years (range, 0.97-12.18), with minimum 2-year follow-up (average, 4.5 ± 2.6 years). 96 of 135 were included in the radiographic PJK study. 89 rib- and 46 spine-based distraction implants were used.Radiographic PJK developed in 38%, and clinical PJK in 18% of patients. Only pre-operative TK >50^{o} increased risk for radiographic PJK (RR: 1.667, P=0.04). Pre-operative spinopelvic parameters did not increase risk for clinical PJK. Regarding quality of life, pelvic incidence –lumbar lordosis (PI-LL) mismatch > ±20^{o} increased risk for poor outcomes through multiple domains while pelvic tilt (PT) >30°, implant type or fusion to pelvis had no effect. Preoperative TK >50º and spine-based distraction construct increased risk of radiographic PJK, and postoperative PI-LL >20º and PT ≥30º increased risk for clinical PJK. Preoperative PI >60° was shown to increase pain.

The effect of spinopelvic parameters on the development of proximal junctional kyphosis in early onset scoliosis

Ozren Kubat, 2021

10. Reference list

1. Marketos SG, Skiadas PK. Hippocrates: The father of spine surgery. Historical Perspective. Spine 1999;24:1381-89.

2. Moe JH. Historical aspects of scoliosis. In: Moe JH, ed. Moe's textbook of scoliosis and other spinal deformities. Philadelphia: Saunders;1987,1.

3. Marketos SG, Skiadas PK. Galen: A pioneer of spine research. Spine 1999;24:2358-62.

4. Cobb JR. Outline for the study of scoliosis. The American Academy of Orthopaedic Surgeons Instructional Course Lectures 1948;5:261-75.

5. Skaggs DL, Guillaume T, El-Hawary R, Emans J, Mendelow M, Smith J. Early onset scoliosis consensus statement. Spine Deform 2015;3:107.

6. Campbell RM Jr, Smith MD, Mayes TC, et al. The characteristics of thoracic insufficiency syndrome associated with fused ribs and congenital scoliosis. J Bone Joint Surg Am 2003;85:399-408.

7. Pehrsson K, Larsson S, Oden A, Nachemson A. Long-term follow-up of patients with untreated scoliosis. A study of mortality, causes of death, and symptoms. Spine 1992;17:1091-96.

8. Muirhead A, Conner AN. The assessment of lung function in children with scoliosis. J Bone Joint Surg Br 1985;67:699-702.

9. Simonds AK, Carroll N, Branthwaite MA. Kyphoscoliosis as a cause of cardio-respiratory failure – pitfalls of diagnosis. Respir Med 1989;83:149-50.

10. Mullassery D, Smith NP. Lung development. Semin Pediatr Surg 2015;24:152-55.

11. Merkus PJ, ten Have-Opbroek AA, Quanjer PH. Human lung growth: a review. Pediatr Pulmonol 1996;21:383-97.

12. deMello DE, Sawyer D, Galvin N, Reid LM. Early fetal development of lung vasculature. Am J Respir Cell Mol Biol 1997;16:568-81.

13. Burri PH. Fetal and postnatal development of the lung. Annu Rev Physiol 1984;46:617-28.

14. Liggins GC. The role of cortisol in preparing the fetus for birth. Reprod Fertil Dev 1994;6:141-50.

15. Jobe AH, Ikegami M. Lung development and function in preterm infants in the surfactant treatment era. Annu Rev Physiol 2000;62:825-46.

16. Hislop A, Reid L. Pulmonary arterial development during childhood: branching pattern and structure. Thorax 1973;28:129-35.

17. Dunnill MS. Postnatal growth of the lung. Thorax 1962;17: 329-33.

18. Weibel ER, Gomez DM. A principle for counting tissue structures on random sections. J Appl Physiol 1962;17:343-48.

19. Davies G, Reid L. Growth of the alveoli and pulmonary arteries in childhood. Thorax 1970;25:669-81.

20. Reid L. Pathologic changes in the lungs in scoliosis. In: Zorab PA, ed. Scoliosis. Springfield:Charles C Thomas;1969,67.

21. De George FV, Fisher RL. Idiopathic scoliosis: genetic and environmental aspects. J Med Genet 1967;4:251-57.

22. Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. Early Hum Dev 1986;13:1-11.

23. Hogg JC, Williams J, Richardson JB, Macklem PT, Thurlbeck WM. Age as a factor in the distribution of lower-airway conductance and in the pathologic anatomy of obstructive lung disease. N Engl J Med 1970:282:1283-87.

24. Thurlbeck WM. Postnatal human lung growth. Thorax 1982;37:564-71.

25. Zeltner TB, Caduff JH, Gehr P, Pfenninger J, Burri PH. The postnatal development and growth of the human lung. I. Morphometry. Respir Physiol 1987;67:247-67.

26. Davies G, Reid L. Effect of scoliosis on growth of alveoli and pulmonary arteries and on right ventricle. Arch Dis Child 1971;46:623-32.

27. Boffa P, Stovin P, Shneerson J. Lung developmental abnormalities in severe scoliosis. Thorax 1984;39:681-82.

28. Berend N, Marlin GE. Arrest of alveolar multiplication in kyphoscoliosis. Pathology 1979;11:485-91.

29. Di Meglio A, Canavese F, Charles YP. Growth and adolescent idiopathic scoliosis: when and how much? J Pediatr Orthop 2011;31Suppl:28-36.

30. Dimeglio A, Bonnel F. Le rachis en croissance. Paris:Springer-Verlag;1990.

31. Bergofsky EH, Turino GM, Fishman AP. Cardio-respiratory failure in kypho-scoliosis. Medicine (Baltimore) 1959;38:263-317.

32. Campbell RM Jr, Hell-Vocke AK. Growth of the thoracic spine in congenital scoliosis after expansion thoracoplasty. J Bone Joint Surg Am. 2003;85:409-20.

33. Owange-Iraka JW, Harrison A, Warner JO. Lung function in congenital and idiopathic scoliosis. Eur J Pediatr 1984;142:198-200.

34. Jones RS, Kennedy JD, Hasham F, Owen R, Taylor JF. Mechanical inefficiency of the thoracic cage in scoliosis. Thorax 1981;36:456-61.

35. Ceballos T, Ferrer-Torrelles M, Castillo F, Fernandez-Paredes E. Prognosis in infantile idiopathic scoliosis. J Bone Joint Surg Am 1980;62:863-75.

36. Thompson SK, Bentley G. Prognosis in infantile idiopathic scoliosis. J Bone Joint Surg Br 1980;62-B:151-54.

37. Sayer LA. Spinal disease and spinal curvature: Their treatment by suspension and the use of the plaster of Paris bandage. London: Smith and Elder:1877.

38. Hibbs RA, Risser JC, Ferguson AB. Scoliosis treated by the fusion operation: An end-result study of three hundred and sixty cases. J Bone Joint Surg Am 1931;13:91-104.

39. Risser JC. The application of body casts for the correction of scoliosis. Instr Course Lect 1955;12:255-59.

40. Cotrel Y, Morel G. The elongation derotation-flexion technique in the correction of scoliosis. Rev Chir Orthop Reparatrice Appar Mot 1964;50:59-75.

41. Harrington PR. Treatment of scoliosis: Correction and internal fixation by spine instrumentation. J Bone Joint Surg Am 1962;44:591-610.

42. Mehta MH. Growth as a corrective force in the early treatment of progressive infantile scoliosis. J Bone Joint Surg Br 2005;87: 1237-47.

43. Sanders JO, D'Astous J, Fitzgerald M, Khoury JG, Kishan S, Sturm PF. Derotational casting for progressive infantile scoliosis. J Pediatr Orthop 2009;29:581-87.

44. Thorsness RJ, Faust JR, Behrend CJ, Sanders JO. Non-surgical management of early onset scoliosis. J Am Acad Orthop Surg 2015;23:519-28.

45. Stagnara P. Cranial traction using the Halo of Rancho Los Amigos. Rev Chir Orthop Reparatrice Appar Mot 1971;57:287-300.

46. Sink EL, Karol LA, Sanders J, Birch JG, Johnston CE, Herring JA. Efficacy of perioperative halo-gravity traction in the treatment of severe scoliosis in children. J Pediatr Orthop 2001;21:519-24.

47. Mubarak SJ, Camp JF, Vuletich W, Wenger DR, Garfin SR. Halo application in the infant. J Pediatr Orthop 1989;9:612-14.

48. MacEwen GD, Bunnell WP, Sriram K. Acute neurological complications in the treatment of scoliosis: A report of the Scoliosis Research Society. J Bone Joint Surg Am 1975;57:404-8.

49. Moe JH, Kharrat K, Winter RB, Cummine JL. Harrington instrumentation without fusion plus external orthotic support for the treatment of difficult curvature problems in young children. Clin Orthop Relat Res 1984;185:35-45.

50. Acaroglu E, Yazici M, Alanay A, Surat A. Three-dimensional evolution of scoliotic curve during instrumentation without fusion in young children. J Pediatr Orthop 2002;22:492-96.

51. Klemme WR, Denis F, Winter RB, Lonstein JW, Koop SE. Spinal instrumentation without fusion for progressive scoliosis in young children. J Pediatr Orthop 1997;17:734-42.

52. Akbarnia BA, Marks DS, Boachie-Adjei O, Thompson AG, Asher MA. Dual growing rod technique for the treatment of progressive early-onset scoliosis: a multicenter study. Spine 2005;30Suppl17:46-57.

53. Skaggs DL, Akbarnia BA, Flynn JM, et al. A classification of growth friendly spine implants. J Pediatr Orthop 2014;34:260-74.

54. Akbarnia BA, Breakwell LM, Marks DS, et al. Dual growing rod technique followed for three to eleven years until final fusion: the effect of frequency of lengthening. Spine 2008;33:984-90.

55. Schulz JF, Smith J, Cahill PJ, Fine A, Samdani AF. The role of the vertical expandable titanium rib in the treatment of infantile idiopathic scoliosis: early results from a single institution. J Pediatr Orthop 2010;30:659-63.

56. Hasler CC, Mehrkens A, Hefti F. Efficacy and safety of VEPTR instrumentation for progressive spine deformities in young children without rib fusions. Eur Spine J 2010;19:400-8.

57. Yamaguchi KT Jr, Skaggs DL, Mansour S, et al. Are rib versus spine anchors protective against breakage of growing rods? Spine Deform 2014;2:489-92.

58. Schmitt D. Insights into the evolution of human bipedalism from experimental studies of humans and other primates. J Exp Biol 2003;206:1437-48.

59. Berge C. Heterochronic processes in human evolution: an ontogenic analysis of the hominid pelvis. Am J Phys Anthropol 1998;105:441-59.

60. Dubousset J. Three-dimensional analysis of the scoliotic deformity. In: Weinstein S, ed. The pediatric spine; principles and practice. New York: Raven Press;1994,479-96.

61. Vialle R, Levassor N, Rillardon L, Templier A, Skalli W, Guigui P. Radiographic analysis of the sagittal alignment and balance of the spine in asymptomatic subjects. J Bone Joint Surg Am 2005;87:260-7.

62. Kozanek M, Wang S, Passias PG, et al. Range of motion and orientation of the lumbar facet joints in vivo. Spine (Phila Pa 1976) 2009;34:689-96.

63. Boseker EH, Moe JH, Winter RB, Koop SE. Determination of „normal“ thoracic kyphosis: a roentgenographic study of 121 „normal“ children. J Pediatr Orthop 2000;20:796-98.

64. Ames CP, Blondel B, Scheer JK, et al. Cervical radiographical alignment: comprehensive assessment techniques and potential importance in cervical myelopathy. Spine (Phila Pa 1976) 2013;38Suppl1:149-60.

65. Faline A, Szadowski S, Berthonnaud E, Fiere V, Roussouly P. Morphological study of the lower cervical curvature: results of 230 asymptomatic subjects. Eur Spine J 2007;16Suppl1:25.

66. Yukawa Y, Kato F, Suda K, Yamagata M, Ueta T. Age-related changes in osseous anatomy, alignment, and range of motion of the cervical spine. Part I: Radiographic data from over 1,200 asymptomatic subjects. Eur Spine J. 2012;21:1492-98.

67. O'Brien MF, Kuklo TR, Blanke KM, Lenke LG, eds. Spinal Deformity Study Group radiographic measurement manual. Memphis: Medtronic Sofamor Danek;2004.

68. Been E, Gomez-Olivencia A, Kramer P. Lumbar lordosis of extinct hominis. Am J Phys Anthropol 2012;147:64-77.

69. Duval-Beaupere G, Schmidt C, Cosson P. A barycentremetric study of the sagittal shape of spine and pelvis: the conditions required for an economic standing position. Ann Biomed Eng 1992;20:451-62.

70. Legaye J, Duval-Beaupere G, Hecquet J, Marty C. Pelvic incidence: a fundamental pelvis parameter for three-dimensional regulation of spinal sagittal curves. Eur Spine J 1998;7:99-103.

71. Roussouly P, Gollogly S, Berthonnaud E, Dimnet J. Classification of the normal variation in the sagittal alignment of the human lumbar spine and pelvis in the standing position. Spine (Phila Pa 1976) 2005;30:346-53.

72. Mac-Thiong J-M, Berthonnaud E, Dimar JR, Betz RR, Labelle H. Sagittal alignment of the spine and pelvis during growth. Spine (Phila Pa 1976) 2004;29:1642-47.

73. Mac-Thiong J-M, Labelle H, Roussouly P. Pediatric sagittal alignment. Eur Spine J 2011; 20Suppl5:586-90.

74. Mangione P, Gomez D, Senegas J. Study of the course of the incidence angle during growth. Eur Spine J 1997;6:163-67.

75. Glattes RC, Bridwell KH, Lenke LG, Kim YJ, Rinella A, Edwards C 2nd. Proximal junctional kyphosis in adult spinal deformity following long instrumented posterior spinal fusion. Incidence, outcomes, and risk factor analysis. Spine 2005;30:1643-49.

76. Kim HJ, Lenke LG, Shaffrey CI, Van Alstyne EM, Skelly AC. Proximal junctional kyphosis as a distinct form of adjacent segment pathology after spinal deformity surgery. A Systematic Review. Spine 2012;37Suppl:144-64.

77. Alanay A, Dede O, Yazici M. Convex instrumented hemiepiphyseodesis with concave distraction: a preliminary report. Clin Orthop Relat Res 2012;470:1144-50.

78. Campbell RM, Jr, Smith MD, Hell-Vocke AK. Expansion thoracoplasty: the surgical technique of opening-wedge thoracostomy. Surgical Technique. J Bone Joint Surg Am 2004;86-A:51-64.

79. Thompson GH, Akbarnia BA, Campbell RM Jr. Growing rod techniques in early-onset scoliosis. J Pediatr Orthop 2007;27:354-61.

80. D'Astous JL, Sanders JO. Casting and traction treatment methods for scoliosis. Orthop Clin North Am 2007;38:477-84.

81. Elsebai HB, Yazici M, Thompson GH, et al. Safety and efficacy of growing rod technique for pediatric congenital spinal deformities. J Pediatr Orthop 2011;31:1-5.

82. Li Y, Gold M, Karlin L. Proximal segmental kyphosis after vertical expandable prosthetic titanium rib insertion. Spine Deform 2013;1:425-33.

83. Reinker K, Simmons JW, Patil V, Stinson Z. Can VEPTR control progression of early-onset kyphoscoliosis? A cohort study of VEPTR patients with severe kyphoscoliosis. Clin Orthop Relat Res 2011;469:1342-48.

84. Shah SA, Karatas AF, Dhawale AA, et al. The effect of serial growing rod lengthening on the sagittal profile and pelvic parameters in early-onset scoliosis. Spine 2014;39:1311-7.

85. Glassman SD, Bridwell K, Dimar JR, Horton W, Berven S, Schwab F. The impact of positive sagittal balance in adult spinal deformity. Spine 2005;30:2024-29.

86. Potter BK, Lenke LG, Kuklo TR. Prevention and management of iatrogenic flat-back deformity. J Bone Joint Surg Am 2004;86-A:1793-808.

87. Takayama K, Nakamura H, Matsuda H. Quality of life in patients treated surgically for scoliosis: Longer than sixteen-year follow-up. Spine 2009;34:2179-84.

88.Vaz G, Roussouly P, Berthonnaud E, Dimnet J. Sagittal morphology and equilibrium of pelvis and spine. Eur Spine J 2002;11:80-7.

89. Cil A, Yazici M, Uzumcugil A, et al. The evolution of sagittal segmental alignment of the spine during childhood. Spine 2005;30:93-100.

90. Mac-Thiong JM, Labelle H, Berthonnaud E, Betz RR, Roussouly P. Sagittal spinopelvic balance in normal children and adolescents. Eur Spine J 2007;16:227-34.

91. Schwab FJ, Lafage R, Glassman SD, et al. Age-adjusted alignment goals have the potential to reduce proximal junctional kyphosis. Spine (Phila Pa 1976) 2017;42:1275-82.

92. Protopsaltis TS, Diebo BG, Lafage R, et al. Identifying thoracic compensation and predicting reciprocal thoracic kyphosis and proximal junctional kyphosis. Spine (Phila Pa 1976) 2018;43:1479-86.

93. Lafage R, Bess S, Glassman SD, et al. Novel virtual modeling of alignment following ASD surgery: establishing relationships between compensatory changes and overcorrection due to proximal junctional kyphosis. Spine J 2015;15;153.

94. El-Hawary R, Sturm PF, Cahill PJ, et al. Sagittal spinopelvic parameters of young children with scoliosis. Spine Deformity 2013;1:343-7.

95. El-Hawary R, Sturm PF, Cahill PJ, et al. Does the type of distraction-based growing system for early onset scoliosis affect post-operative sagittal alignment? J Child Orthop 2011;5:387-401.

96. El-Hawary R, Sturm PF, Cahill PJ, et al. Sagittal spinopelvic parameters help predict the risk of proximal junctional kyphosis for children treated with posterior distraction based implants. J Child Orthop 2011;5:387-401.

97. Joukhadar N, Kubat O, Heflin J, et al. Superior extension of upper instrumented vertebrae in distraction based surgery: a surrogate for clinically significant proximal junctional kyphosis. Spine Deform 2019;7:371-75.

98. Al Khudairy A, Gauthier L, Heflin JA, et al. Reliability of proximal junctional kyphosis measurements for young children with scoliosis. Spine Deform 2014;2:448-53.

99. Corona J, Matsumoto H, Roye DP, Vitale MG. Measuring quality of life in children with early onset scoliosis: development and initial validation of the early onset scoliosis questionnaire. J Pediatr Orthop 2011;31:180-85.

100. Matsumoto H, Williams B, Park HY, et al. The Final 24-item early onset scoliosis questionnaires (EOSQ-24): validity, reliability and responsiveness. J Pediatr Orthop 2018;38:144-51.

101. Barrett KK, Andras LM, Tolo VT, Choi PD, Skaggs DL. Measurement variability in the evaluation of the proximal junction in distraction-based growing rods patients. J Pediatr Orthop 2015;35:624-27.

102. Astur N, Flynn JM, Ramirez N, et al. The efficacy of rib-based distraction with VEPTR in the treatment of early-onset scoliosis in patients with arthrogryposis. J Pediatr Orthop 2014;34:8-13.

103. El-Hawary R, Sturm P, Cahill P, et al. What is the risk of developing proximal junctional kyphosis during growth friendly treatments for early-onset scoliosis? J Pediatr Orthop 2017;37:86-91.

104. Wang Y, Kawakami N, Tsuji T, et al. Proximal junctional kyphosis following posterior hemivertebra resection and short fusion in children younger than 10 years. Clin Spine Surg 2017;30:370-76.

105. Chen X, Chen ZH, Qiu Y, et al. Proximal junctional kyphosis after posterior spinal instrumentation and fusion in young children with congenital scoliosis: a preliminary report on its incidence and risk factors. Spine (Phila Pa 1976) 2017;42:1197-203.

106. Watanabe K, Uno K, Suzuki T, et al. Risk factors for proximal junctional kyphosis associated with dual-rod growing-rod surgery for early-onset scoliosis. Clin Spine Surg 2016;29:428-33.

107. Kim YJ, Lenke LG, Bridwell KH, et al. Proximal junctional kyphosis in adolescent idiopathic scoliosis after 3 different types of posterior segmental spinal instrumentation and fusions: incidence and risk factor analysis of 410 cases. Spine (Phila Pa 1976) 2007;32:2731-38.

108. Lee GA, Betz RR, Clements DH 3rd, Huss GK. Proximal kyphosis after posterior spinal fusion in patients with idiopathic scoliosis. Spine (Phila Pa 1976) 1999;24:795-99.

109. Lafage R, Bess S, Glassman S, et al. Virtual modeling of postoperative alignment after adult spinal deformity surgery helps predict associations between compensatory spinopelvic alignment changes, overcorrection, and proximal junctional kyphosis. Spine (Phila Pa 1976) 2017;42:1119-25.

110. Senteler M, Weisse B, Snedeker JG, Rothenfluh DA. Pelvic incidence-lumbar lordosis mismatch results in increased segmental joint loads in the unfused and fused lumbar spine. Eur Spine J 2014;23:1384-93.

111. Rothenfluh DA, Mueller DA, Rothenfluh E, Min K. Pelvic incidence-lumbar lordosis mismatch predisposes to adjacent segment disease after lumbar spinal fusion. Eur Spine J 2015;24:1251-58.

112. Sun XY, Zhang XN, Hai Y. Optimum pelvic incidence minus lumbar lordosis value after operation for patients with adult degenerative scoliosis. Spine J 2017;17:983-89.

113. Maruo K, Ha Y, Inoue S, et al. Predictive factors for proximal junctional kyphosis in long fusions to the sacrum in adult spinal deformity. Spine (Phila Pa 1976) 2013;38:1469-76.

114. Gomez JA, Lee JK, Kim PD, Roye DP, Vitale MG. "Growth friendly" spine surgery: management options for the young child with scoliosis. J Am Acad Orthop Surg 2011;19:722-27.

115. Chen Z, Li S, Qiu Y, et al. Evolution of the postoperative sagittal spinal profile in early-onset scoliosis: is there a difference between rib-based and spine-based growth-friendly instrumentation? J Neurosurg Pediatr 2017;20:561-66.

116. Wang J, Zhao Y, Shen B, et al. Risk factor analysis of proximal junctional kyphosis after posterior fusion in patients with idiopathic scoliosis. Injury 2010;41:415-20.

117. Helgeson MD, Shah SA, Newton PO, et al. Evaluation of proximal junctional kyphosis in adolescent idiopathic scoliosis following pedicle screw, hook or hybrid instrumentation. Spine (Phila Pa 1976) 2010;35:177-81.

118. Kim YJ, Bridwell KH, Lenke LG, Kim J, Cho SK. Proximal junctional kyphosis in adolescent idiopathic scoliosis following segmental posterior spinal instrumentation and fusion: minimum 5-year follow-up. Spine (Phila Pa 1976) 2005;30:2045-50.

119. Kim HJ, Yagi M, Nyugen J, et al. Combined anterior-posterior surgery is the most important risk factor for developing proximal junctional kyphosis in idiopathic scoliosis. Clin Orthop Relat Res 2012;470:1633-39.

120. Ghailane S, Pesenti S, Peltier E, Choufani E, Blondel B, Jouve JL. Posterior elements disruption with hybrid constructs in AIS patients: is there an impact on proximal junctional kyphosis? Arch Orthop Trauma Surg 2017;137:631-5.

121. Cammarata M, Aubin CE, Wang X, Mac-Thiong JM. Biomechanical risk factors for proximal junctional kyphosis: a detailed numerical analysis of surgical instrumentation variables. Spine 2014;39:E500-07.

122. Anderson AL, McIff TE, Asher MA, Burton DC, Glattes RC. The effect of posterior thoracic spine anatomical structures on motion segment fixation stifness. Spine (Phila Pa 1976) 2009;34:441-46.

123. Inaparthy P, Queruz JC, Bhagawati D, Thakar C, Subramanian T, Nnadi C. Incidence of proximal junctional kyphosis with magnetic expansion control rods in early onset scoliosis. Eur Spine J 2016;25:3308-15.

124.Schwab FJ, Blondel B, Bess S, et al. Radiographical spinopelvic parameters and disability in the setting of adult spinal deformity: a prospective multicenter analysis. Spine (Phila Pa 1976) 2013;38:803-12.

125.Schwab FJ, Ungar B, Blondel B, et al. Scoliosis Research Society-Schwab adult spinal deformity classification: a validation study. Spine (Phila Pa 1976) 2012;37:1077-82.

126. Diebo BG, Ferrero E, Lafage R, et al. Recruitment of compensatory mechanisms in sagittal spinal malalignment is age and regional deformity dependent: a full-standing axis analysis of key radiographical parameters. Spine (Phila Pa 1976) 2015;40:642-49.

127. Mendoza-Lattes S, Ries Z, Gao Y, Weinstein SL. Proximal junctional kyphosis in adult reconstructive spine surgery results from incomplete restoration of the lumbar lordosis relative to the magnitude of the thoracic kyphosis. Iowa Orthop J 2011;31:199-206.

128. Campbell RM Jr, Smith MD. Thoracic insufficiency syndrome and exotic scoliosis. J Bone Joint Surg Am 2007;89Suppl1:108-22.

129. Vitale MG, Matsumoto H, Roye DP Jr, et al. Health-related quality of life in children with thoracic insufficiency syndrome. J Pediatr Orthop 2008;28:239-43.

130. Caldas JC, Pais-Ribeiro JL, Carneiro SR. General anesthesia, surgery and hospitalization in children and their effects upon cognitive, academic, emotional and sociobehavioral development - a review. Paediatr Anaesth 2004;14:910-15.

131. Butler RW, Rizzi LP, Handwerger BA. Brief report: the assessment of posttraumatic stress disorder in pediatric cancer patients and survivors. J Pediatr Psychol 1996;21:499-504.

132. Schwering KL, Febo-Mandl F, Finkenauer C, Rimé B, Hayez JY, Otte JB. Psychological and social adjustment after pediatric liver transplantation as a function of age at surgery and of time elapsed since transplantation. Pediatr Transplant 1997;1:138-45.

133. Matsumoto H, Williams BA, Corona J, et al. Psychosocial effects of repetitive surgeries in children with early-onset scoliosis: are we putting them at risk? J Pediatr Orthop 2014;34:172-78.

134. Flynn JM, Matsumoto H, Torres F, Ramirez N, Vitale MG. Psychological dysfunction in children who require repetitive surgery for early onset scoliosis. J Pediatr Orthop 2012;32:594-99.

11. Short Curriculum Vitae

I was born February 20th 1984 in Zagreb. I am married and a father of one daughter, Maša. I received my medical degree from the University of Zagreb School of Medicine in year 2008. In year 2009, I started working at the Department of orthopaedic surgery as a research fellow, moved on to residency in 2011 and gave my board exam in January 2016.

During my orthopaedic training I have actively participated in many national and international scientific meetings. I have received a number of scholarships, awarded by the European Paediatric Orthopaedic Society, European Federation of Orthopaedics and Traumatology, American Academy of Orthopaedic Surgeons and Pediatric Orthopedic Society of North America. I have finished a Research Fellowship in Halifax, Canada, as well as a Clinical Fellowship in Tel Aviv, Israel. During my training I've visited many International centres of excellence, like the Great Ormond Street Hospital, Hospital for Special Surgery, Bristol Royal Hospital for Children, and Wrightington Hospital.

As the first co-investigator I was part of a team of surgeons awarded with research funding from the Scoliosis Research Society in year 2015 for a research project on early onset scoliosis that produced 3 scientific papers as well as this PhD thesis. I am a member of the editorial board of Bone & Joint 360 and serve as a reviewer for a number of scientific journals in the field of orthopaedics.