METOPIC SYNOSTOSIS- SURGICAL RESULTS AND PERINATAL ASPECTS

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To my parents.

"There is something fascinating about science.
One gets such wholesale returns of conjecture out
of such a trifling investment of fact."

- Mark Twain.

METOPIC SYNOSTOSIS-
SURGICAL RESULTS AND PERINATAL ASPECTS

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ABSTRACT

Metopic synostosis (MS) is the second most common type of craniosynostosis (CS). This thesis aimed to evaluate surgical results in children operated for MS, their perinatal outcomes and potential etiological risk factors.

Methods: In study I, we measured the distribution of frontal and intracranial volume ratio at 6-months postoperatively (at spring removal) to determine relapse. Study II measured the degree of bony temporal hollowing before and after surgery. Study III assessed three grading scales for complication reporting in craniofacial surgery. Studies IV and V used data from the Swedish Birth Register to study perinatal outcomes in collaboration with the Netherlands (study IV) and evaluate aetiological factors in CS (study V).

Results: Study I found no significant differences in volume ratios between spring removal and the 3-year follow-up. Study II revealed that surgery reduced temporal deformity. Study III identified complication rates as follows: Clavien–Dindo, 7.2%; Leeds, 13.1%; Oxford, 8.1%. Study IV found higher Caesarean section rates in children born with MS and sagittal synostosis (SS). MS was associated with higher rates of assisted reproductive technology (ART), breech, and pre-term birth. Study V revealed maternal age, male sex, and breech as independent risk factors for CS, whereas male sex, twins, and conception by ART were risk factors for MS.

Conclusions: Relapse is not the cause of low frontal volume ratio, surgery eradicates two-thirds of temporal deformity, Oxford grading is suitable for reporting complications in CF surgery, SS and MS children are at risk of higher rates of Caesarean sections, and we identified ART, twins and male sex as independent risk factors for MS.

Keywords: metopic synostosis, craniosynostosis, temporal hollowing, ART, perinatal outcomes, complications.

SAMMANFATTNING PÅ SVENSKA

Kraniosynostos innebär en för tidig slutning av en eller flera av skallens tillväxtsömmar. Missbildnigen uppkommer i fosterlivet och redan vid födseln är skallens form förändrad. Vid metopikasynostos är det suturen i pannan som slutits för tidigt och det leder till att pannan blir plogformad och att ögonen sitter tätt. Behandlingen är kirurgisk.

Målsättningen med denna avhandling är att belysa resultaten av kirurgi för metopikasynostos och att undersöka om det finns några speciella förhållanden under graviditet och förlossning för dessa barn. Avslutningsvis belyser också avhandlingen vilka riskfaktorer som kan identifieras för uppkomsten av kraniosynostos.

I delarbete I visas att den omfördelning av skallens volym som operationen åstadkommer står sig bra vid tre års ålder. Det finns altså inga tecken på återfall. I det andra delarbetet har graden av korrektion i tinningregionen mätts. Operationen syftar till att göra den plogformade pannan mjukt rundad och arbetet visar att två tredjedelar av formdefekten korrigeras men att det finns en bit kvar till att få pannans form helt normal. I delarbete III har vi undersökt tre olika system för att klassificera komplikationer till kraniofacial kirurgi. Mindre omfattande kirurgi ger färre komplikationer och ett system utarbetat i Oxford var det som lämpade sig bäst för att klassificera komplikationerna. I delabete IV noteras att barn med metopikasynostos oftare än andra kommit till genom assisterad befruktning och att deras graviditetslängd är något kortare än förväntat. I det sista delarbetet visas att hög ålder hos mamman är en riskfaktor för kraniosynostos och tvillingar är vanligare än förväntat hos barn med metopikasynostos. Studien visar också att uppkomstmekanismen för kraniosynostos inte är trängsel i fosterlivet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Bhatti-Söfteland M**, Maltese G, Tarnow P, Wikberg E, Bernhardt P, Kölby L, *The Degree of Surgical Frontal Volume Correction in Metopic Synostosis Determines Long-Term Outcomes,* Journal of Craniofacial Surgery: Volume 28, Issue 5, July 2017

II. **Bhatti-Söfteland M**, Maltese G, Tarnow P, Hagmarker L, Wikberg E, Bernhardt P, Kölby L, *Temporal Deformity Objectively Measured Before and After Surgery for Metopic Synostosis: Retrusion Rather than Hollowing*, Journal of Craniofacial Surgery, Volume 28, Issue 7, October 2017

III. Paganini A*, **Bhatti-Söfteland M***, Fischer S, Kölby D, Hansson E, O'Hara J, Maltese G, Tarnow P, Kölby L, *In search of a single standardised system for reporting complications in craniofacial surgery: A comparison of three different classifications*, Journal of Plastic Surgery and Hand Surgery, Volume 53, Issue 6, June 2019.* Shared first authorship

IV. Cornelissen MJ, **Söfteland M**, Apon I, Ladfors L, Mathijssen IMJ, Cohen-Overbeek TE, Bonsel GJ, Kölby L, *Perinatal complications in patients with unisutural craniosynostosis: An international multicentre retrospective cohort study,* Journal of Cranio-Maxillofacial Surgery, Volume 45, Issue 11, Nov 2017

V. **Bhatti-Söfteland M**, Ladfors L, Tarnow P, Maltese G, Kölby L, *Evaluating etiological risk factors for craniosynostosis; parental age, IVF, plurality and fetal constraint.* Manuscript

CONTENTS

ABBREVIATIONS

AOR	Adjusted odds ratio
ART	Assisted reproductive technology
CF	Craniofacial
CI	Confidence interval
CS	Craniosynostosis
CT	Computed tomography
FOA	Fronto-orbital advancement
FC	Foetal constraint
GCR	Gothenburg craniofacial registry
GCC	Gothenburg Craniofacial Centre
ICP	Intracranial pressure
ICSI	Intracytoplasmic sperm injection
ICV	Intracranial volume
IQ	Intelligence quotient
IVF	In vitro fertilisation
IUI	Intrauterine insemination
MBR	Medical Birth Register
MS	Metopic synostosis
NCS	Non syndromic craniosynostosis
OR	Crude odds ratio
Q-IVF	National Quality Register of Assisted Reproduction
SCB	Statistics Sweden
SD	Standard deviation
SS	Sagittal synostosis
TH	Temporal hollowing

INTRODUCTION

Craniosynostosis

The relatively large size of the human brain at birth is a defining feature of evolution. A term infant is born with 33% of their adult brain volume, which increases dramatically in the early postnatal period. The skull consists of several flat bones that keep up with this expansion to protect the growing brain. Correspondingly, intracranial volume (ICV) reaches 77% of adult size by two years of age, at which point growth slows down and is more or less complete by seven years of age[1].

Growth of the developing cranium occurs at the cranial sutures (Figure 1). Rapid bone formation occurs at these fibrous joints, allowing the skull bones to enlarge in width and grow apart. Sutures, thus, are required to maintain a delicate balance in laying down bone but without ossifying. Disruption of this process results in craniosynostosis (CS), which is a premature closure of one or more of the sutures *in utero*. Growth then ceases along the length of the suture, with the two bone plates becoming fused. The enlarging brain drives compensatory overgrowth at the open sutures, leading to progressive distortion of the skull shape. This causes a characteristic skull deformity depending on the type and number of sutures involved (Figure 2).

In humans, another hallmark of evolution is the development of an upright gait, which has resulted in a narrower maternal pelvis. The net effect is a neonate with a relatively large head negotiating a tight fit at birth. Open cranial sutures facilitate labour by allowing temporary deformation of the skull bones. This is called molding and adapts the foetal head for a successful vaginal delivery. CS leads to altered head shape and size, which may theoretically interfere with this process resulting in adverse perinatal outcomes[2,3].

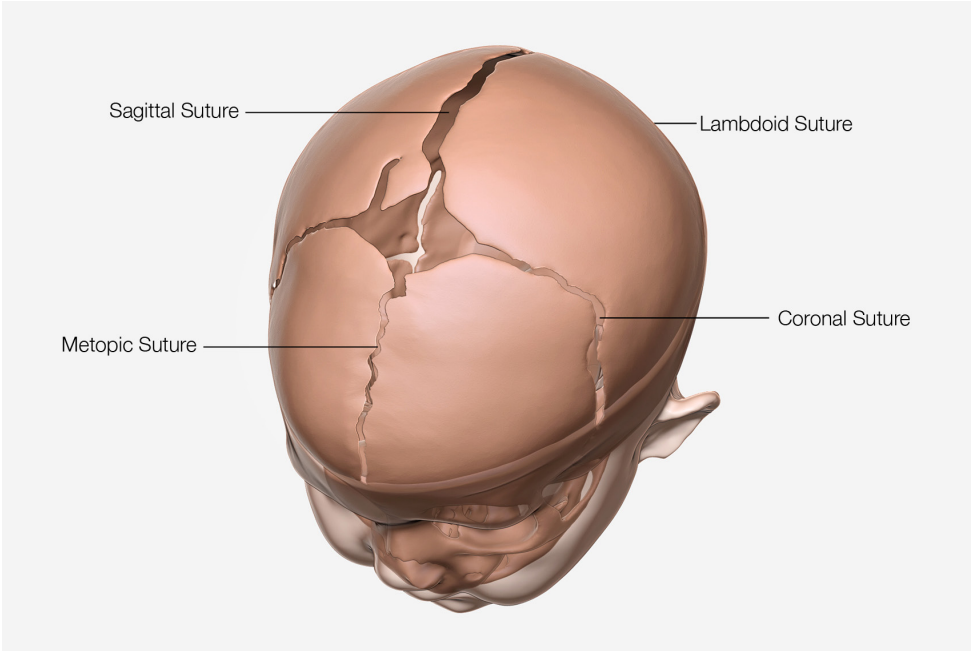

Figure 1: 3D reconstruction of the skull and open sutures. Illustration by Niclas Löfgren.

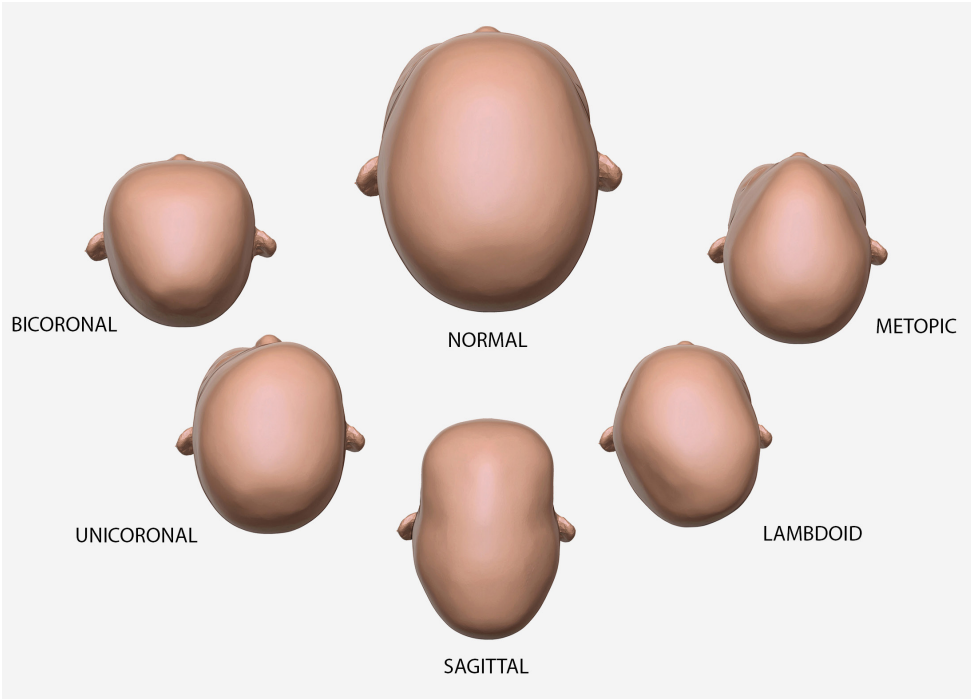

Figure 2: 3D reconstruction of normal head shape and the different types of CS. Illustration by Niclas Löfgren.

CS is an isolated event in 79% of cases and part of a CS syndrome in 21% of cases[4]. Multiple sutures are usually involved in syndromic CS, with other associated anomalies, e.g. midface retrusion, hearing loss and syndactyly[5]. Additionally, there is an increased risk of elevated intracranial pressure (ICP), which may lead to headaches, atrophy of the optic nerve, blindness, and even death if left untreated[6]. In contrast, in nonsyndromic craniosynostosis (NCS), premature suture fusion is the main finding and primarily impacts the skull shape.

The most common nonsyndromic form is sagittal synostosis (SS), comprising 50-60%, followed by metopic synostosis (MS) at 25%[7]. Both types are three times more frequent in males. Incidence of CS is usually quoted as 3.1-6.4/10,000 live births[8]. However, in recent years, an increased incidence of CS (particularly MS) has been noted in both Europe and Australia[8,9]. A similar trend is seen in Norway[10] and Sweden, with a recent study from our centre reporting the incidence of CS as 7.7/10,000 live births in Sweden[7].

The aetiology of NCS is mostly unknown, although several theories have been proposed. Intrauterine head constraint in late pregnancy is often mentioned in the literature based on a higher number of twins with CS[11,12]. Moreover, observational studies have linked NCS with maternal smoking[13], thyroid disease[14], and parental age[15]. Genetic alterations play a significant role in the aetiology of syndromic CS, but to date, <1% of NCS can be explained by it[16]. Additionally, family history may play a role, with a 2% to 5% chance of recurrence in siblings[4]. This higher risk of recurrence and the higher incidence of concordance in monozygotic twins (61% vs. 5.3% in dizygotic twins) both suggest an as yet unrecognised genetic influence[17].

Treatment of CS is by surgery, with indications and timing dependent on the type of CS. Surgery is usually performed earlier in the syndromic child, depending on the clinical picture. Cranioplasties to widen the skull and relieve intracranial pressure or shunting for hydrocephalus may be necessary as early as eight weeks. Often, several complex procedures on the midface and skull are required with a higher risk of complications.

In NCS, the principal goal of surgery is to remodel the skull in order to increase volume, normalise the appearance to allow psychosocial adjustment and prevent the risk of increased ICP. The timing of surgery varies widely between centres. Early surgery (< 1 year) has the potential advantages of better bone pliability and enhanced re ossification of surgical defects. In contrast, late surgery may have the benefit of a more stable reconstruction due to thicker bone and possibly decreased growth inhibition and tendency to relapse[18].

Prenatal and postnatal growth of the skull

The development of the skull starts at 6 weeks of gestation, when a sheet of mesenchyme surrounds the brain. In terms of growth, this development can be subdivided into the vault-neurocranium and the cartilaginous cranial base (the chondrocranium), which form via two distinct processes. The cranial base forms by the same mechanism as other bones in the body, i.e., endochondral ossification. During this process, growth occurs through cartilage, similar to the growth plates of long bones, where cartilage first hypertrophies and then gradually ossifies. However, the neurocranium accomplishes this directly by intramembranous ossification (Figure 3), which lacks a cartilage precursor stage and instead forms through direct differentiation of mesenchymal cells into osteoblasts. The consequence of these different mechanisms is noted in achondroplasia, a genetic disorder where the primary feature is dwarfism. Defective endochondral ossification results in stunted body growth while unaffected membranous ossification leads to a disproportionately large head.

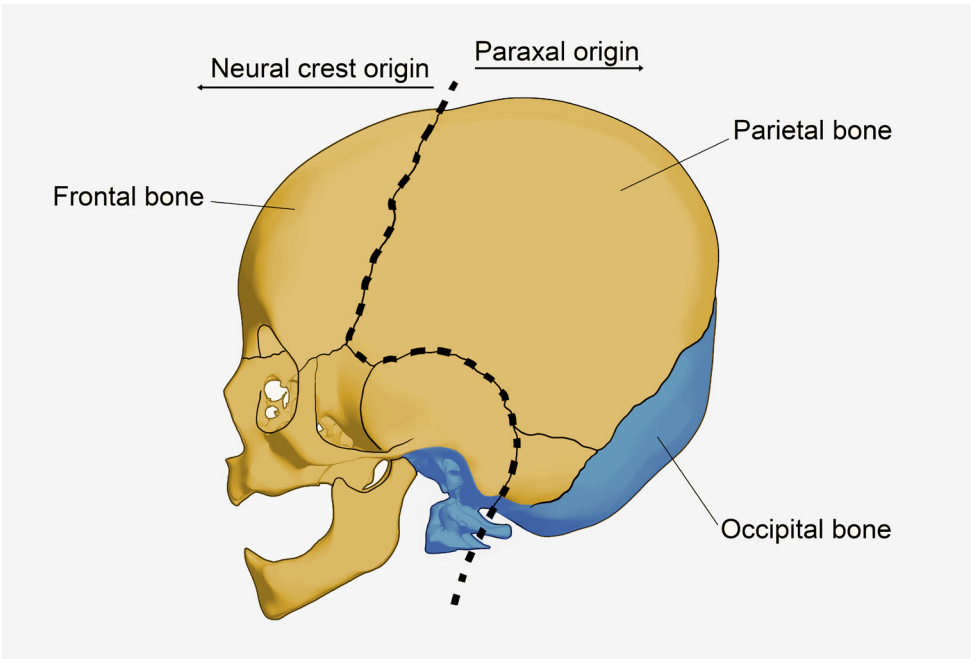

Figure 3: Intramembranous ossification (yellow) and endochondral ossification (blue). The dotted line shows the different origins. Illustration by Niclas Löfgren.

Bone is secreted as needle-like spicules that progressively radiate outward but do not fuse at the junction with other bones. As growth proceeds, the bone fronts approximate each other, and suture formation is initiated at the junction. In the vicinity of the suture, a group of mesenchymal cells differentiate into osteoblasts that synthesise bone matrix along the edges. Thus, sutures differ from cartilaginous growth plates, which are growth centres with intrinsic growth potential, whereas sutures are growth sites that depend on surrounding stimuli from the expanding brain[19].

Embryologically, skull bones and sutures derive from different embryonic origins. The parietal and occipital bones are mainly derived from the paraxial mesoderm, whereas the frontal bones, meninges, and the brain are formed from neural crest cells (Figure 3). The metopic suture also originates exclusively from the neural crest. By contrast, the sagittal and coronal sutures are of mixed origin formed at the interface of the neural crest and mesoderm-derived tissue[19]. Suture formation starts with the metopic suture at 15 weeks, followed by the coronal suture at 16 weeks, and the sagittal and lambdoid sutures at 18 weeks[20]. Physiological closure of skull sutures starts with the metopic suture, which is the only one that closes in the first year of life. The other sutures close much later, beginning with the sagittal sutures, which close between age 22 and 40, and ending with the lambdoid sutures around 70 years of age. This sequential timing is unique and often utilised in forensic anthropology for age estimation.

The flat bones of the skull are initially thin and unilaminar. At ~4 years of age, they develop into an outer and inner table of compact bone with spongy bone (diploe) in the middle. Active sutural growth is responsible for the postnatal increase in skull size, whereas remodelling allows for changes in curvature and the formation of sinuses. Bone resorption occurs from the inner surface and is coupled with deposition on the outer surface. This remodelling is highly effective in the earlier years, as observed by surgeons using metal wires or plates for reconstruction on the growing skull. Anything placed on the outer surface of the skull migrates and, on reoperation at a later age, is discovered on the inner surface.

Surgery from then to now

Historically craniofacial surgery had a bleak start. Neurosurgeons made the first attempts at suture release in the 1890s. These initial endeavours carried a 50% mortality rate, and surgery for this indication was largely abandoned for the next decades. The 1920s saw renewed interest in suture release and, while achieving better survival, results were suboptimal due to rapid reossification. Attempts to

keep the suture open included inserting a silicone strip and even treating dura with Zenker's solution (a fixative with mercuric chloride used previously in pathology to fix and decalcify bone marrow biopsies). Severe iatrogenic complications followed in the form of seizures, late infection, and bone loss[21].

The field changed in the 1960s with the debut of Paul Tessier, a French plastic surgeon, who pioneered several extensive craniofacial (CF) procedures. Recognising the need for an intracranial approach, he enlisted the cooperation of Guiot, a neurosurgeon, and catalysed a shift from treating CS alone to a team approach[22]. Following this collaborative approach, the next significant development came from the Gothenburg Craniofacial Centre (GCC) in Sweden, with the development of dynamic springs[23]. This was closely followed by the first endoscopic surgery and the use of distraction osteogenesis in CF surgery[24,25]. Placement of an internal steel spring at the edge of the bone keeps the suture from reossifying and allows the growing brain to modulate dynamic correction. Springs are now used in several countries, with additional refinements in design made by the Erasmus Medical Centre in Rotterdam and the Great Ormond Street Hospital in London.

At the GCC, a multidisciplinary team has cared for children with CS since the 1970s. The team now comprises plastic surgeons, neurosurgeons, maxillofacial surgeons, anesthesiologists, orthodontists, neuroophthalmologists, and a dedicated team psychologist, speech therapist, and coordinators. CF care in Sweden has been centralised since 2012 to two centres (Gothenburg and Uppsala), with a catchment area of 10.3 million people. All patients operated for CF surgery at the GCC are registered in the Gothenburg Craniofacial Registry (GCR), which was established in 1990 and contains data on >1500 patients.

METOPIC SYNOSTOSIS

At birth, the frontal bone consists of two halves joined by the metopic suture (metopon-forehead in Greek). The metopic suture is distinct, in that it is of purely neural crest origin, the first one to close, and the only suture in humans to obliterate physiologically. Fusion usually starts at 2 months of age, although evidence from 3D ultrasounds shows that it begins to close as early as 32 weeks of gestation[26]. In rare cases, the metopic suture can persist into adult life (a phenomenon known as metopism). Complete closure occurs between 3 to 9 months of age; it begins at the nasion and continues upward in a zip-like manner toward the fontanelle, resulting in one frontal bone[27].

The metopic suture is responsible for the lateral growth of the frontal bones. Premature fusion, results in a narrow, triangular forehead (trigonocephaly) with a palpable midline ridge (Figure 4). Additionally, there is recession of the superior orbital rim along with temporal retrusion and hypotelorism. The eyebrows are raised medially, and epicanthal folds may be present. The anterior fontanelle may be absent, and in the parietal region, there is compensatory growth that causes biparietal widening[28]. The diagnosis is based on clinical examination and computed tomography (CT).

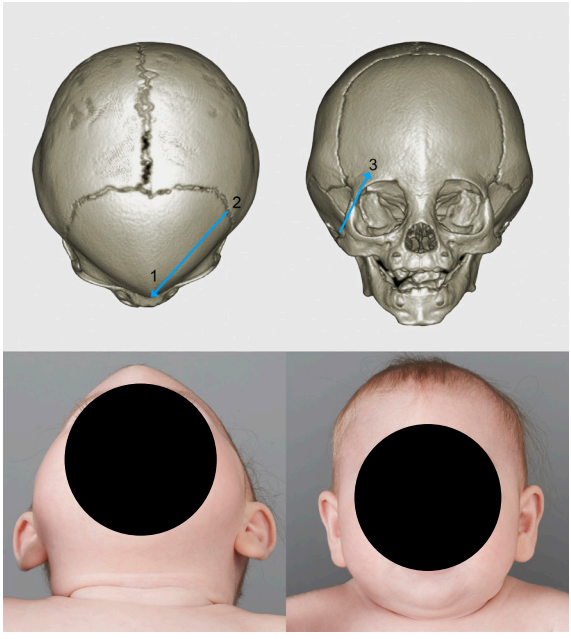

Figure 4: 3D CT image (above) and photographs (below) of a child with MS. Typical features include a midline ridge (1), triangular forehead with medial displacement of the lateral part of the frontal bone (2) and hypotelorism with upsloping orbits (3).

MS can present with varying degrees of severity (Figure 5), ranging from mild to severe. In some infants, a palpable thickening may occur over the suture during the normal physiological closure and is known as a metopic ridge[29]. This may be confused with mild MS. Parents usually give a history of it not being present at birth but appearing a few months later. Clinically, apart from a palpable ridge, other signs of true synostosis are lacking. The overall head shape is normal, eyes are not close-set, and there is no temporal retrusion. Moreover, compensatory biparietal changes are also missing. Metopic ridge is a benign condition that remodels and disappears during infancy.

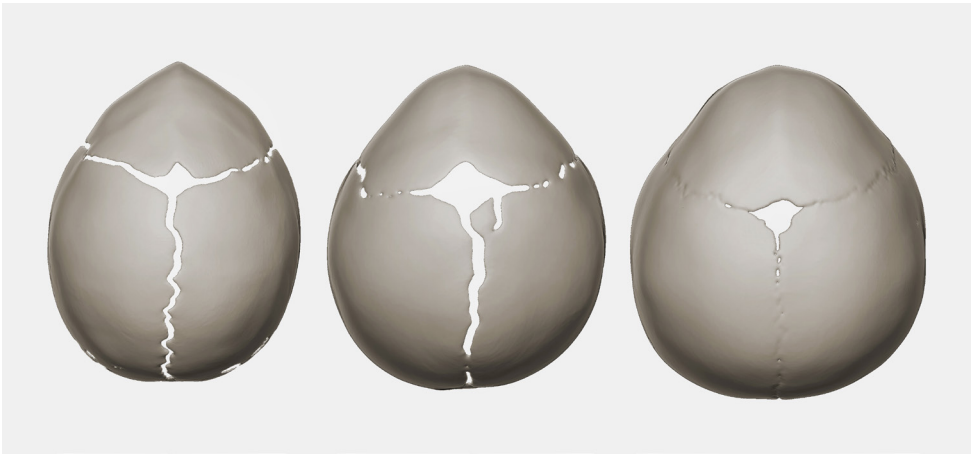

Figure 5: 3D CT skull reconstruction illustrating MS of varying severity from severe (left) to mild (right).

Etiopathogenesis

In recent years a rise in the prevalence of CS, specifically MS[30], has been noted. MS incidence was initially determined at approximately 0.7 in 10,000 live births in the 1990s but is now estimated at 1.8 in 10,000 live births[7]. There are no explanations as yet. Improved diagnostics probably play some part, but most studies show similar detection rates over the previous decades[8]. There is some concern that misdiagnosis of the metopic ridge is the cause[28]. Environmental factors such as maternal drug use and nutritional status are also mentioned in the literature. Folic acid is prescribed prenatally to prevent neural tube defects as it assists in the closure of midline structures. MS is a midline structure; therefore, the increase in incidence has been linked to folic acid supplementation, but studies have not been able to support this claim[31]. Maternal exposure to anticonvulsants, specifically valproate is a known risk factor, resulting in anomalies in 9.4% of cases. In foetal valproate syndrome, MS is a hallmark feature along with spina bifida, congenital heart defects, oral clefts, and limb anomalies[32].

Genetic alterations in MS, are sporadic, but studies suggest a possible familial component. Compared to other NCS, MS reportedly shows the highest rate of positive family history at 6%[32]. Additionally, *SMAD6* mutations were recently detected in the midline sagittal and metopic synostosis, with the highest prevalence (6%) found in MS[16].

Of all NCS, MS shows the highest association with other congenital anomalies and syndromes[32]. Syndromes involving MS are rare and include the following[5,33].

- Frydman: an autosomal dominant condition described in an Israeli family, where the original progenitor had affected descendants by two wives. It is characterised by omphalocele, large phallus, and MS with normal intellectual development.
- Say–Mayer: an X-linked disorder characterised by short stature, MS, and developmental delay.
- Opitz C: MS with limb and visceral anomalies, severe learning disabilities, hypotonia, and poor prognosis.
- Syndromes with chromosomal abnormalities with MS have been reported in chromosomes 3q, 7p, 9p, 10p, 11q, and 22q, with developmental delay being a consistent feature. MS sporadically has been linked to other identifiable syndromes, e.g. MS, due to imprinting in a child with Silver–Russell syndrome[33]. At the GCC, MS has been occasionally noted as part of syndromic CS in Saethre–Chotzen and Crouzon syndrome.

Raised intracranial pressure

One of the general indications for surgery in NCS is the prevention of raised ICP. If left untreated, elevated ICP can lead to optic atrophy and neurocognitive delay. Renier et al. (1982) linked ICP and neurocognitive delay to growth restriction of the skull[6]. A higher ICP correlated to neurocognitive impairment, and surgery subsequently normalised ICP. A commonly drawn conclusion has been that surgery improves both conditions, with this concept dictating clinical practice for most CF centres. However, a causal relationship between ICP and growth restriction of the skull in NCS has not been confirmed. Patients with SS show normal ICV; however, despite surgery, 9% still have a tendency towards high ICP[34].

Detection of raised ICP in small children is a contentious topic, as are the actual values that define elevate pressure[35]. The gold standard is direct intracranial monitoring, but this involves general anaesthesia and risks infection, cerebrospinal fluid leakage and bleeding. Therefore fundoscopy to screen for papilledema is

more often used. It is noninvasive and reliably indicates raised ICP, but with a sensitivity of only 22% in young children[36], its absence does not exclude it.

In children with MS, it has been traditionally believed that elevated ICP occurs in 8% to 33% of cases[37]. Recent studies, however, challenge these findings and note a much lower prevalence. In 2017, two high-volume centres presented results in a large patient cohort. The Erasmus Centre in Rotterdam evaluated ICP with fundoscopy and occipitofrontal circumference, finding it raised in 1.9% of cases before surgery, and 1.5% after surgery on long term follow-up[37]. Potential underestimation by fundoscopy due to the low sensitivity was countered by combining with head measurements as stagnation is a reliable sign for raised ICP. The Oxford Craniofacial Unit identified raised ICP in 1% of patients before surgery, and in 2.9% of cases upon follow-up[38]. Both groups reported late onset of recurrence at ~4 years of age.

Neurodevelopmental aspects

Premature fusion of a suture directly impacts skull growth and shape, thereby affecting ICV; however, whether this affects neurodevelopment and the role of raised ICP remain unclear. The following theories form the basis of why the neurocognitive function is believed to be affected by premature synostosis.

First, the assumption is that the impact on cerebral function is dependent on the severity of mechanical restriction of the frontal lobes. A previous study suggested severe restriction as a strong predictive factor of behavioural and cognitive problems[39]; however, later studies showed no difference in intelligence quotient (IQ) scores between mild and severe cases[40]. Second, MS is a marker of primary anomalous brain development where cognitive problems, and CS originates from a shared primary malformation[41]. Third, chronically raised ICP in NCS causes neurocognitive delay. Although Renier et al. (1982) suggested an association between raised ICP and low IQ, this has been refuted[35].

The frontal region is tasked with impulse inhibition, executive function and personality. Given the anatomic position of MS over the frontal lobe, its association with cognitive impairment and behavioural problems has been the subject of numerous studies. If lack of consensus is a recurrent theme in CF surgery, then it is particularly prominent with regard to MS and neurocognitive function. Findings are conflicting for several reasons. Confounders such as paternal education and income usually predict better performance in children, and such socioeconomic factors are rarely considered[42]. Studies have been known

to paint a rosy picture due to the selection bias of highly educated parents; after cranioplasties, children with SS are reported to achieve a mean IQ level typical of a college graduate[43]. Age at testing is another important factor, as most tests are not suitable for small children. Development differences may be overlooked, and it is challenging to correlate early motor development with subsequent cognitive problems. Moreover, most of these problems are not apparent before school age, when children are exposed to more intellectually and socially demanding surroundings, and there are few studies on this age group.

In general, children with MS have a mean IQ within the normal range[44]. However, the proportion of these children with low IQ scores is higher than the normal population[45](IQ<70; 9% vs 2.5%). Additionally, developmental delay is more likely in the presence of other extracranial anomalies (e.g., limb or cardiac defects), as observed in foetal valproate syndrome, where developmental delay is a consistent feature[33,45].

Behavioural problems appear to be overrepresented in MS [46,47], and some studies report a higher incidence of attention-deficit/hyperactivity disorder (ADHD) in MS children[48]. However, ADHD is not fully diagnosable before 7 years of age, and children in these studies are mostly younger. Nevertheless, there appears to be a correlation between IQ and behavioural problems associated with MS. Children with a lower IQ are more prone to behavioural problems[45]; a finding also well-documented in the general population.

It is important to note that these findings were all based on studies of operated children. Therefore, the extent to which surgery affects neurodevelopmental outcomes remains unclear. Some studies have presented data on children that were conservatively managed usually due to milder form of MS. Kelleher et al. (2006) reported a higher rate of behavioural issues in both operated and unoperated children with MS[46] while Bellew et al. (2015) found signs of nonverbal learning difficulties regardless of whether the patient had undergone surgery[50].

SURGICAL TECHNIQUES

Surgery for MS aims to expand the frontal region and correct hypotelorism. CF surgery is a relatively young speciality, and this is reflected in that every centre has its own preferred technique for MS. Most centres report acceptable results; however, normal or near-normal forehead configuration without recurrence on long-term follow-up is rarely reported.

Surgical options include open, endoscopic, and distraction techniques.

Open techniques

Open surgery involves cranioplasty, which includes a variation of fronto-orbital advancement (FOA) with or without correction of hypotelorism. FOA expands the frontotemporal area and advances the supraorbital bar in order to widen the forehead.

At the GCC, MS is treated by cranioplasty and FOA using two standard surgical techniques, depending upon the age of the child at the time of surgery. In older children (>6 months), a bone graft is used with FOA to correct hypotelorism; however, this technique does not sufficiently correct the hypotelorism. Hypotelorism is best corrected dynamically with near normalisation by the use of springs; therefore, in children <6 months of age, the standard procedure is FOA with springs[51]. Subsequent removal of the springs entails a second short, usually outpatient procedure after 6-months.

Cranioplasty with spring

For this procedure, a zig-zag bicoronal incision is made, followed by subgaleal dissection which is converted to subperiosteal dissection at 3- to 4-cm above the supraorbital rim. The supraorbital nerves are then dissected and preserved, temporal muscle is raised in the subperiosteal plane, markings are made, and perioperative photography is performed (Figure 6). Following dural dissection, the frontal bone flap is removed, and careful haemostasis is performed between the dura and bone. With adequate protection of orbital content and the brain, supraorbital osteotomies are performed with a sagittal saw. The supraorbital bar is advanced using the tongue-in-groove technique to obtain visible overcorrection at the temporal region.

The frontal bone is divided and affixed laterally, leaving a central gap. Several barrel stave osteotomies are carried out in the parietal region, and the bone is out fractured perpendicular to the coronal suture. An osteotomy is performed at the midline down to the nasofrontal suture preserving the medial part of the orbital roof. A spring (length 12 cm, diameter 1.2 mm, 8N) is placed via burr holes in the glabellar region to correct hypotelorism.

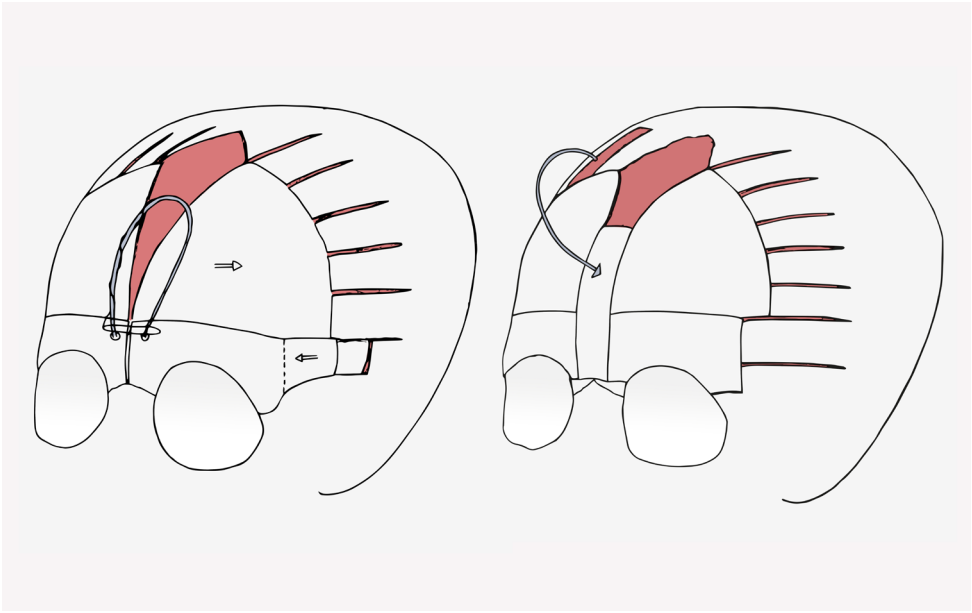

Figure 6: Cranioplasty with a spring (left) and with a bone graft (right). Illustration: Dr. Peter Tarnow.

Cranioplasty with a bone graft

The supraorbital bar contains the lateral aspect of the sphenoid ridge at the temporal region passing through the frontozygomatic suture and the orbital roof. For this technique, the bar is completely released, and then remodelled back table using an interpositional bone graft (10–12mm wide), harvested from the right parietal region, between the forehead flaps. A chisel is placed in the midline of the glabella and gently tapped to separate the nasal bones. The remodelled forehead is then secured with the bone graft wedged in position with resorbable plates (Figure 6). Temporalis muscles are reattached with resorbable sutures, and the skin incision is closed with resorbable sutures and without drains. Recent refinements have been made to this procedure; forehead flaps are now scored with a mill burr on the inner surface to achieve a rounder shape, and the supraorbital bar is scored laterally.

The procedure usually takes ~120 mins, with an average postoperative stay of 5 days. All children receive blood transfusion intraoperatively. The first follow-up occurs 1 month after surgery, with all children examined clinically at ages 3 and 5 years. Postoperative CT is performed at the time of spring removal and the 3-year follow-up. Photographs and 3D pictures are obtained at all visits by clinical photographers.

Endoscopic techniques

Endoscopic techniques are used at some centers and rely on performing early suturectomy at 2 to 3 months of age followed by helmet moulding. Helmets need to be worn 23 h/day for up to 1 year or longer. Centres with long term follow-up report shorter surgical times (66.7 min), lower blood loss, and comparable volume correction[52,53].

Distraction techniques

The use of distractors in NSC is a relatively recent development. Although presently not a typical technique used for MS, a systematic review reported that it had been performed on 27 patients. Three to four distractors are placed during a median surgical time of 250 min, resulting in a hospital stay of 12 days for MS, which is higher than corresponding numbers for open surgery[54].

EVALUATION OF SURGICAL RESULTS

Intracranial volume

ICV measurement offers insight into the available space for the brain to expand and can be used to assess gains in volume after surgery compared to normal controls. ICV can be measured using skull CT scans either manually, automatically, or semiautomatically with no significant difference in results[55].

The volume of interest in MS is the frontal region, as this is the target area of surgery. The MATLAB program used in the first study was developed at the GCC to evaluate total and frontal ICV in MS children[56] (Figure 7). The semiautomated technique segments axial CT slices and relies on algorithms to exclude bone gaps and soft tissue. Hounslow units are pre-set for bone and soft tissue. A pixel starts as a seed point and grows using the region-growing algorithm till it hits bone, outlining the intracranial area. This semiautomated technique allows the user to manually mark the coronal suture in order to determine the frontal volume.

Figure 7: 3D reconstruction of total ICV (left) and the frontal volume (right).

All CT slices are loaded into the program (300 slices if .625mm thick). The first slice above the foramen magnum is manually chosen as the starting slice and the slice just beneath the inner surface of the vertex as the end-point. The coronal sutures are manually marked. The program then calculates the entire intracranial volume and the frontal volume of the fossa anterior by multiplying the area of each slice with slice thickness. Each measurement takes about 5-10 mins per patient.

Temporal deformity

Temporal hollowing (TH) is a contour deformity usually observed as a triangular depression in the frontotemporal region in children with MS and unicoronal synostosis (Figure 8). The area contains the temporalis muscle and fat pads as well as the underlying bone where the lateral expansion of the bar is carried out. TH is often referred to as a postoperative finding in the literature. It may occur postoperatively in neurosurgical procedures requiring a coronal approach due to iatrogenic damage to vascularity or innervation. However, in MS, the deformity is present before the surgery and recurs to varying degrees[57].

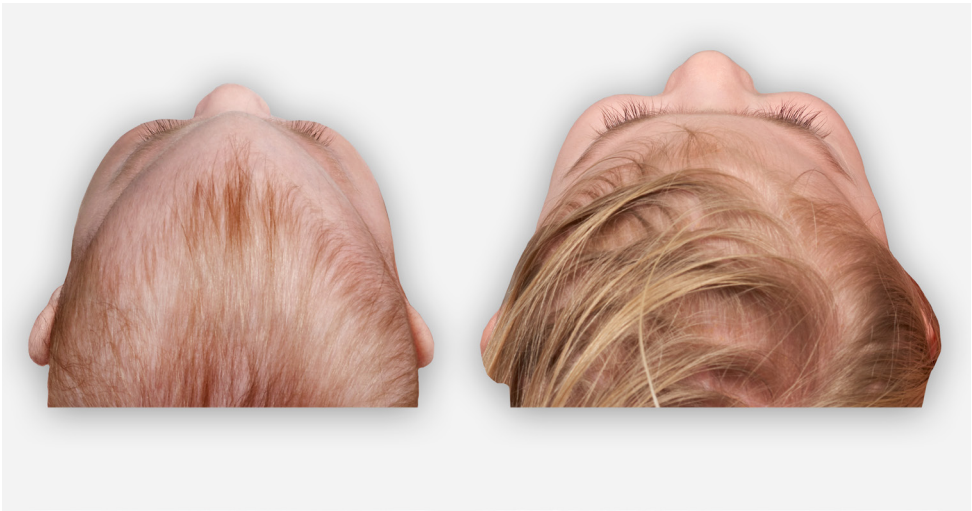

Figure 8: Temporal retrusion before surgery (left) and after surgery at three years of age (right).

Most surgical techniques, including ours, aim for some degree of subjective overcorrection in order to prevent TH; however, overcorrection can only be accomplished to a certain extent, as it is ultimately limited by tight skin closure. As a rule, aesthetic results are usually good over the short term, with recurrence only recognised on long-term follow-up[58]. The indication for surgery is for aesthetic purposes, and the defect is usually augmented with a bone substitute or lipofilling. Revision surgery rates vary between 8% and 20%[38,59].

The aetiology of temporal deformity is not fully understood. The components that can be responsible include fat, temporalis muscle, and the underlying bone. One explanation is an intrinsic growth inhibition of the bone. A retrusion in the region is part of the initial picture; therefore, both pre- and post-deformities could signify some degree of genetically determined return to the phenotype[60]. Soft-tissue components have been studied in unicoronal synostosis, where only one

side is affected, thus enabling the unaffected side to be used in the same patient for control measurements. The superficial fat pad does not appear to play a role in this deformity, and only a slight reduction in muscle thickness has been reported after surgery[61]. The extent of the bony deformity has not been previously measured.

Evaluation of TH or other postoperative stigmata is usually performed using the Whitaker classification[62], which applies a grade based on the increasing need for revisional surgery (Table 1). Although the main strength of this classification is its simplicity, it is highly subjective, and its grading eventually depends on the eye of the beholder.

Table 1. Whitakers classification. From *Wes et al.*[58]

Grade	Description
I	No refinements or surgical revisions considered advisable or necessary by the surgeon or the patient.
II	Soft-tissue or lesser bone-contouring revisions desirable whether performed or not.
III	Major alternative osteotomies or bone-grafting procedures needed or performed.
IV	Major procedure duplicating or exceeding in extent the original surgery necessary.

Complications

CF procedures are complex with osteotomies that traverse the intracranial space, sinuses and orbits; and are thus prone to a range of complications. Complication rates have improved significantly in terms of mortality and morbidity since Whitaker et al. (1979) honestly reported their complication rate of 16.5% and mortality of 1.6-2.2%[63]. Causes of mortality in CF literature vary from excessive blood loss to airway obstruction and even pulmonary embolism, while visual loss, neurological deficit, and wound infections contribute to morbidity rates[64]. MS-specific complications align with these findings, with mortality being a rare but documented occurrence[58]. Other complications associated with MS may involve problems with wound healing due to tight wound closure after skull expansion.

Although uniform registration of adverse events has been carried out in general surgery for years, no such attempt has been made for CF surgery. Therefore no consensus exists for a single classification system, and adverse events are often reported in a descriptive manner[65].

PERINATAL ASPECTS

Perinatal outcomes

Open sutures at birth facilitate molding of the foetal skull for a successful vaginal delivery (Figure 9). Premature synostosis causes fusion of skull bones that may theoretically lack the pliability required for an effective labour. A higher rate of emergency Caesarean section in children with CS was first reported in 2005[66]. Traumatic deliveries in CS children result in adverse maternal and fetal impact. Higher rates of induced labour, malpresentations and assisted vaginal delivery are reported. Additionally, vaginal deliveries have a higher rate of cephalhematomas and maternal perineal ruptures[2]. According to the World Health Organization, an ideal rate for Caesarean sections is between 10% and 15%; however, in CS children, this rate is closer to 30%[2,67]. Furthermore, emergency Caesarean section rates are reported to be 17-20%[2], resulting in worse Apgar scores and a four-fold likelihood of admission to the intensive care unit[68]. The overall prognosis, however, is improved if CS is detected prenatally as it allows for better obstetric planning[68].

Prenatal diagnosis is rare and usually only occurs in syndromic cases and as a consequence of other coexisting anomalies[69]. In Sweden, only one ultrasound is performed during pregnancy which is the anomaly scan at 18–20 weeks. Theoretically, since CS commences around 15-18 weeks of gestation, detection is possible at the anomaly scan[69].

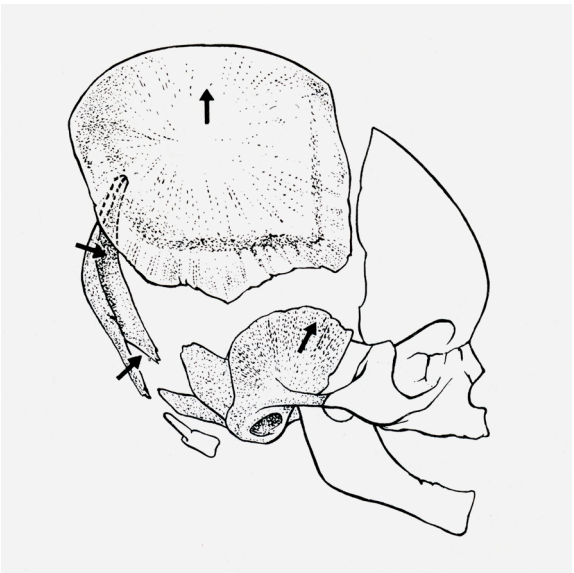

Figure 9: Molding describes the change in the shape of the foetal head as it adapts to the pelvic outlet. From Cohen et al[70].

Assisted reproductive technology

The first child born following *in vitro* fertilisation (IVF) in Sweden was in 1982, and since then, 4% of births annually are the result of assisted reproductive technology (ART). Infertility can depend on male or female factors but remains unexplained in ~20% of cases. Female factors include ovulation disorders, while male factors include poor semen quality. Additionally, lifestyle factors include obesity, smoking, and advanced maternal age[74].

ART comprises intrauterine insemination (IUI) or IVF. In IUI, processed motile sperm are placed directly into the uterus, whereas in standard IVF, sperm and oocytes are mixed in a culture medium, allowing sperm to enter and fertilise an egg (Figure 10). In cases utilising poor quality sperm, intracytoplasmic sperm injection (ICSI) is performed using ejaculated or microsurgically retrieved sperm, and embryos can be either implanted or cryopreserved for later use. Ovarian stimulation promotes the ovulation of mature follicles to increase the chances of conception and can be used alone or in combination with IUI and IVF.

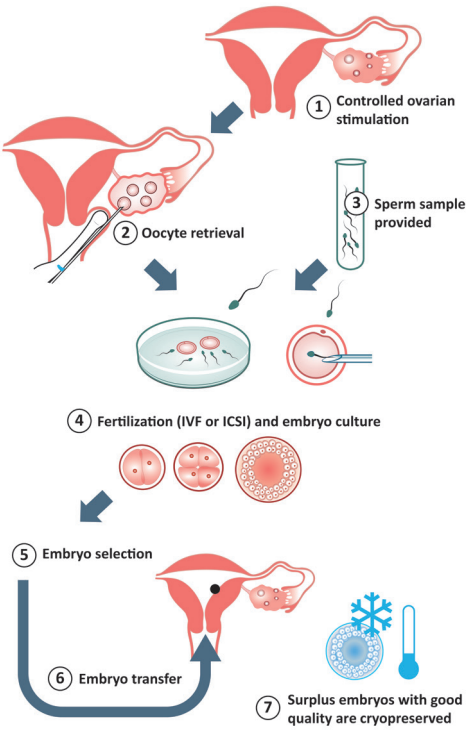

Figure 10: Steps in the IVF procedure. Illustration by Jan Funke[74]

Technical aspects of ART technique such as culture media, cryopreservation and thawing could influence the gamete/embryo during a period when it is theoretically vulnerable to epigenetic changes[71]. In addition, ICSI bypasses natural sperm selection and can potentially introduce culture medium during the injection phase. Compared with spontaneously conceived children, there is an increased risk for congenital anomalies in children born via ART[72] (2.9% vs 3.4%). A correlation between CS and ART was first reported in a small study by Reefhuis et al.[73](2003), with subsequent studies also reporting a possible association (Table 2).

Table 2: Overview of studies on association between ART and CS.

Author and year of publication	No. of children with CS	Type of synostosis studied	No. of children conceived by ART	Maternal age >35 (n)
Reefhuis[73], 2003	99	NSC	10	15
Källen[75], 2005	398	All CS	14	83*
Singh[76], 2010	103	Only MS	4	10
Ardalan[77], 2012	70	All CS	9	NS
Cornelissen[3], 2017	424	MS and SS	38	NS
Hormozi[78], 2021	200	NCS	8	NS
Junaid[79], 2022	417	All CS	11	67*
Søfteland et al. unpublished, 2022	814	All CS, MS and SS	45	143

*= included mothers aged 35

NS= data on mothers >35 not specified

Swedish birth register

There is a long tradition in Swedish healthcare for implementing reliable and comprehensive databases. The Swedish birth register (MBR) was established in 1973 and includes all children born alive and stillborn after week 22. Reporting to the MBR is mandatory, and data are collected on the mother and child from antenatal, delivery, and neonatal care. Variables for smoking were added in 1983, and information concerning infertility treatment in 1995. There are ~100,000 children born in Sweden annually, with data available for 97% to 99.5% of the births[80]. Missing data vary according to individual variables, e.g., 4–9% of information on smoking is missing. Information concerning the use of ART in Sweden is present in the MBR, and since 2007, all infertility treatments have also been registered in the National Quality Register of Assisted Reproduction (Q-IVF). Data regarding paternity, however, is not recorded in the MBR. This information is usually registered in Statistics Sweden (SCB), a national database with data on demographics.

FOETAL CONSTRAINT THEORY

The foetal head constraint (FC) theory, is first mentioned in 1918[81] but gained traction since the three works by Graham et al. (1980) with dysmorphologist David W. Smith. According to the FC theory, CS occurs in late pregnancy due to mechanical compression of the skull. Factors related to FC include early descent, multiple births, uterine malformations, breech malpresentation, macrosomia, and nulliparity[82-85].

In their case report, the authors implicate FC as the cause of MS in two children; one wedged in a bicornuate uterus and another in breech position in a set of monozygotic triplets[82]. Early descent into the pelvis (4 to 6 weeks before delivery) is implicated as the main aetiology for SS[84], and the more common right-sided unicoronal synostosis[83](71%). In SS, the mechanism proposed is that the prolonged constraint in the lateral dimesnsion reduces the growth stretch on the sagittal suture leading to synostosis. The authors also posit that if the head descends early in the most common vertex position (left occiput transverse), the right coronal suture experiences constant strain against the pubic bone but not the left as it lies against sacral prominence. Similarly, the male predominance in CS is explained in terms of FC, given that male foetuses have a larger head size that is more prone to constraint, as is the 2.6-fold higher rate of CS twin births[11].

Animal models to test the FC hypothesis have produced conflicting results. A sheep model simulated FC by intrauterine plate fixation of the coronal suture but only resulted in deformational changes and not synostosis[86]. However, FC simulated in a murine model led to both deformation and fusion of squamous and coronal sutures[87,88].

SUMMARY OF STUDIES

	Study I	Study II	Study III	Study IV	Study V
Study design	Retro-spective	Retro-spective	Retro-spective	Retro-spective	Retro-spective
No. of patients	20	120	641	424	814
Controls	60	160	-	1,954,141	2,228,126
Data source(s)	GCR	GCR	GCR	GCR, MBR, Dutch perinatal registry	GCR, MBR
Primary outcome(s)	Frontal-to-total volume ratio at the time of spring removal in children operated with springs	Area of bony temporal deformity before and after surgery	Test three different complication grading scales for suitability in CF surgery	Rate of medically assisted labour	Evaluating etiological risk factors for CS: parental age, IVF and smoking
Secondary outcome			Analyse complications at GCC over a 10-year period	ART, term of birth and foetal position	Evaluating FC-related factors: twins, breech, and nulliparity

STUDY I

The degree of surgical frontal volume correction in metopic synostosis determines long-term outcomes

Aim

The aim was to investigate the distribution of ICV at 6 months postoperatively and determine whether the low frontal to total volume ratio at 3-year follow-up was due to relapse.

Patients (n=20)

This was a retrospective study of children operated for MS between 2002 and 2008.

Controls (n-60)

For every child, two sex- and age-matched controls were identified from children that had undergone CT for trauma or neurological evaluation.

Calculation of intracranial volume (ICV)

A previously designed MATLAB program was used for semiautomatic segmentation of axial CT slices. Total ICV and frontal volume were calculated before surgery, at the time of spring removal, and at 3 years of age, with the frontal-to-total ICV ratio presented as a percentage.

Statistical analysis

Student's paired-samples *t*-test was used to compare frontal-to-total ICV ratios between patients and controls, as well as the difference in ratios between 6-months post-surgery and at follow-up at 3-years of age. A $P < 0.05$ was considered significant.

Results

The preoperative frontal-to-total ICV ratio was 9.8 ± 1.3% [mean ± standard deviation (SD)], which increased to 11.8 ± 2.4% at spring removal and was 11.6 ± 1.9% at 3 years of age. In age-matched normal children, the ratio was 14.4 ± 1.9% preoperatively, 15.3 ± 2.2% at spring extraction, and 13.4 ± 1.4% at three years of age.

The ratio was significantly lower for cases than controls at all three time points ($P < 0.001$), and there were no significant differences in the ratios between the two postoperative values (i.e., at spring removal and 3-year follow-up).

STUDY II

Temporal deformity objectively measured before and after surgery for metopic synostosis: retrusion rather than hollowing

Aim

The aim of this study was to objectively measure the temporal deformity in children with MS before and after surgery in two different procedures.

Patients (n=120)

This was a retrospective study of all children operated for MS between 2002 and 2014 with available CT scans performed preoperatively and/or at the 3-year follow-up. Depending on age, two surgical techniques were used. If the children presented at <6 months of age, they were operated with FOA and a spring, whereas children aged >6 months were operated with a bone transplant.

Controls (n=160)

For every child, a sex- and age-matched control was identified from children that had undergone CT for trauma or neurological evaluation. The age range for the controls in the preoperative group was ±30 days and ±90 days in the follow-up group. Exclusion criteria for controls were prematurity, hydrocephalus, the presence of shunts, and severe cranial fractures. These were excluded as they may affect cranium vault form and size.

Area calculation

The bony temporal deformity was measured as an area using a previously published MATLAB program and compared with controls.

Statistical analysis

All results were presented as the mean ± SD, and a paired Student's *t* test was performed to compare the average differences between cases and controls.

Results

In total, 160 CT scans were included from 120 patients (male: female ratio = 4:1).

The temporal deformity was significantly reduced by both techniques ($P < 0.001$). In the spring group, the deformity was reduced from 3.6 ± 1.9% to 1.0 ± 1.2% and in the bone-transplant group from 3.3 ± 1.4% to 1.1 ± 0.8%.

In the preoperative group, maximal and the minimal temporal retrusion was 8% and 1%, respectively while in the postoperative group, it was 3% and –4.7% (the negative value signified that the temporal region in the patient was larger than that in the control).

The difference in area between cases and controls indicated four distinct schematic patterns of temporal retrusion. The patterns varied depending on the relationships in contour between each case and the respective control in both the temporal and anterior parietal region.

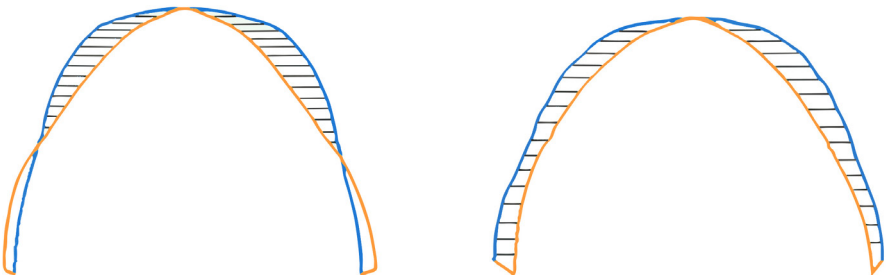

Figure 11: Two types of temporal retrusion representing the difference between a case (orange) and control (blue).

STUDY III

In search of a single standardised system for reporting complications in craniofacial surgery: a comparison of three different classifications

Aim

The aims of this study were to determine the applicability of three different gradings of complications in CF surgery and review complications at the GCC over a 10-year period.

Patients (n=641)

This was a retrospective study of all patients who underwent surgery between 2006 and 2015 and that were identified from the GCR.

Data collection

Two investigators independently reviewed all patient records for complications, which were then graded according to the three classifications: Clavien–Dindo, Leeds, and Oxford. Patient demographics, perioperative details, length of hospital stay, and postoperative outcomes were noted from admission to postoperative follow-up at 1 month. Any events that occurred after discharge (e.g. wound-healing problems) but communicated via phone/email were also included. Because data were retrospectively analysed, late sequelae were included, which extended the evaluation period to 10 years of complications.

Statistical analysis

The overall complication rate was calculated as the number of complications per procedure since several patients underwent two-stage procedures.

Results

One thousand and twenty-three consecutive CF procedures were identified in 641 patients.

The complication rate was 7.2%, 13.1% and 8.1%, according to Clavien–Dindo, Leeds and Oxford, respectively (Tables 3–6).

Table 3: Overview of complications per procedure.

Procedures (no.)	Leeds	Clavien - Dindo	Oxford
Cranioplasty (398)	98	43	45
Spring assisted cranioplasty (187)	26	11	15
Mid face corrections (18)	14	9	10
Orbital correction (7)	0	0	0
Extraction of foreign material (357)	8	4	3
Secondary corrections with PMMA (41)	13	5	8
Nose reconstruction (10)	3	2	3
Miscellaneous (5)	1	0	1
No. of complications (rate %)	163(13.1%)	74(7.2%)	85(8.1%)

Table 4: Clavien–Dindo classification[89].

Clavien-Dindo		n
I	Deviation from the normal postoperative course without need of intervention	19
II	Complication requiring pharmacological treatment (e.g., blood transfusion)	27
III	Complications requiring surgical, endoscopic, or radiological intervention	
IIIa	Complication requiring surgical intervention without anaesthesia	6
IIIb	Complications requiring surgical intervention with anesthesia	13
IV	Life-threatening complication (including complications of the central nervous system) that requires management in a high dependency, or intensive therapy unit	
IVa	Complications involving single organ dysfunction (including dialysis)	6
IVb	Complication involving multiorgan dysfunction	3
V	Death	0
Total		74

n: no of complications.

Table 5: Leeds classification[65].

Leeds			n
0. Perioperative	A	Excessive blood transfusion (>60 ml/kg)	6
	B	Significant anaesthetic instability or complications	31
	C	Unplanned surgical intervention during index admission	5
1. In-patient	A	w/ normal LOS	39
	B	w/ prolonged LOS (>2 SD)	11
	C	w/ exceptionally prolonged LOS (>2 wks)	7
2. Out-patient not requiring readmission	A	≤30 days since discharge	9
	B	>30 days since discharge	16
3. Out-patients requiring readmission	A	Nonsurgical ≤30 days since discharge	3
	B	Nonsurgical >30 days since discharge	0
	C	Surgical ≤30 days since discharge	6
	D	Surgical >30 days since discharge	25
4. Unexpected long-term deficit	A	Resolved by six months	0
	B	Present at six months	5
5. Mortality		A inpatient or ≤30 days since discharge B >30 days since discharge	0
Total			163

LOS, length of stay.

Table 6: Oxford classification[90].

Oxford		n
1	No delay in discharge, reoperation, or long-term sequelae	35
2	Delay in discharge but no further operation required	14
3	Reoperation but no long-term sequelae	33
4	Unexpected long-term deficit or neurological impairment; permanent disability	3
5	Mortality	0
Total		85

STUDY IV

Perinatal complications in patients with unisutural craniosynostosis: an international multicentre retrospective cohort study

Aim

The aim of this study was to evaluate perinatal outcomes in MS and SS patients from two European countries.

Patients (n=424)

All children with SS or MS operated between 2006 and 2012 at the GCC, and the Erasmus Craniofacial Centre in Rotterdam were included. For Swedish children, parents of 244 patients were approached for inclusion. The child's personal identity number was linked to that of the mother in order to allow maternal data to be extracted from the MBR. For the Netherlands, 270 parents were approached for inclusion. A questionnaire on pre- and perinatal data was sent to all parents and then cross-referenced with the national perinatal registry.

Controls (n=1,954,141)

All live births in the two countries between 2006-2012 were included as controls.

Statistical analysis

Continuous data were compared using an independent *t* test, and categorical data were compared using a chi-squared test. Fisher's exact test was used instead of the chi-squares test when appropriate. If applicable, Bonferroni correction was performed to correct for multiple testing.

Results

For the Swedish cohort, 10 MS and 14 SS patients could not be reached or did not want to participate, resulting in 78 MS and 142 SS Swedish patients (participation rates: 89% and 91%, respectively). The control population of this cohort comprised a maximum of 754,981 individuals, depending on the variable in question.

For the Netherlands, 22 MS patients and 44 SS patients could not be reached or refused to participate. Consequently, the Dutch cohort comprised 74 MS and 130 SS patients (participation rates: 77% and 75%, respectively). The control population of this cohort comprised a maximum of 1,199,160 individuals, depending on the variable in question.

There were no significant differences in the sex distribution of MS and SS patients between countries. Moreover, no significant differences existed concerning maternal age between the mothers of patients and the control populations in either country.

Mean gestational age at birth was significantly lower for MS patients than controls ($P = 0.0001$). The rate of breech malpresentation was significantly higher in MS patients than in SS patients and controls ($P = 0.003$). A significantly higher rate of preterm births was observed in MS patients, whereas post-term births were more frequent in SS patients ($P < 0.001$). Mean birth weight was lower in MS patients ($P = 0.01$) and higher in SS patients ($P = 0.02$), and head circumference was larger in SS patients than in the control population (36.2 cm vs. 34.9cm; $P < 0.0001$).

The start of labour and the delivery method differed between countries. For the Netherlands, the rates of induced labour and non-elective Caesarean section were significantly higher in MS and SS patients as compared with controls.

For the Swedish cohort, rates of elective and non-elective Caesarean section were higher in both patient groups as compared with the control population. Additionally, the rate of uncomplicated delivery was lower in MS (55%) and SS (61%) patients relative to the control population (75%) ($P < 0.001$).

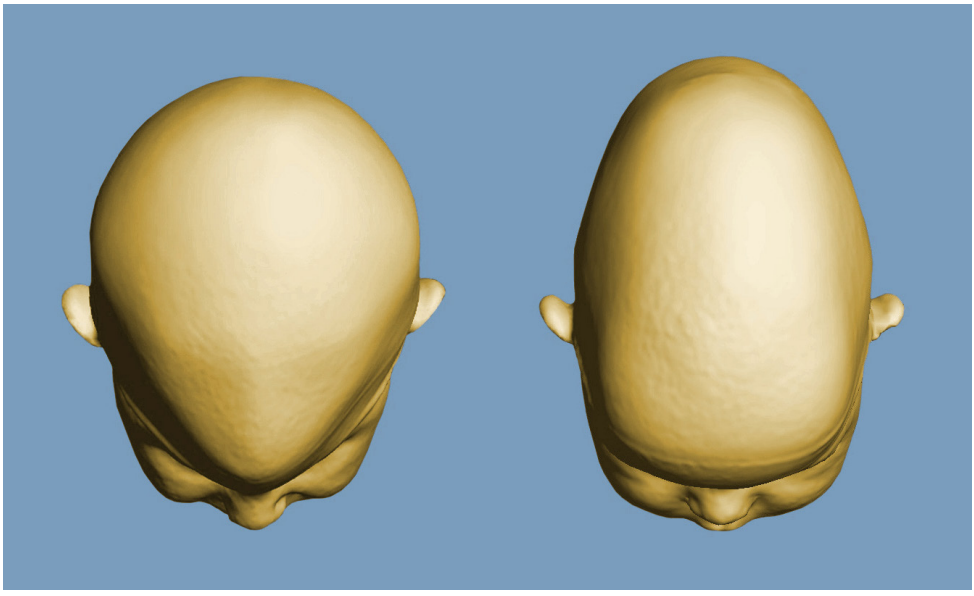

Figure 12: Head shapes in MS children (left) and SS children (right).

STUDY V

Evaluating etiological risk factors for craniosynostosis; parental age, IVF, twins and fetal constraint

Aim

The aim of this study was to evaluate parental age, ART, plurality, and foetal constraint as possible risk factors in a population-based study design.

Patients (n-1187)

The retrospective study included clinical data from the GCR for all children operated for CS between 1973 and 2016.

Controls (2,228,126)

Data on all live births in Sweden from the same time period was extracted from the MBR and paternal age from Statistics Sweden (SCB).

Data collection

The personal identity numbers of the children were linked to those of their mother in order to allow maternal data to be extracted from the MBR and paternal age from SCB.

Exposure variables retrieved from the MBR included age, smoking status, use of ART, number of births, parity, and foetal malpresentation. Because reliable data on smoking status and ART variables were not available until 1995, data processing was limited to 1995 to 2016.

Statistical analysis

Univariate and multivariate analyses of risk factors for CS were performed, and diagnosis-specific subgroup analysis was performed for SS and MS.

Results

CS cases (n = 814) and controls (n = 2,228,126) were identified between 1995 and 2016. Maternal age was an independent risk factor for CS, adjusted odds ratio (AOR) = 1.02; (CI: 1.01–1.04), whereas paternal age and smoking had no effect. Twins were more common in CS (3.7%) than controls (2.9%), and breech malpresentation was significantly higher in CS (4.9%) relative to controls (3.7%). Nulliparity was not an independent risk factor.

For SS, maternal age AOR = 1.02; (CI: 1.00–1.04) and male sex AOR = 3.07; (CI: 2.43–3.88) were independent risk factors. For MS, ART was an independent risk factor AOR = 1.79; (CI: 1.08–2.98), as were twins AOR = 1.98; (CI: 1.11–3.53) and male sex AOR = 4.18; (CI: 2.94–5.95).

Ethical approval

Studies I-IV in this thesis were approved by the Regional ethics committee in Gothenburg (Regionala etikprövningsnämnden i Göteborg), Sweden (Study I-III: Dnr 784-11, Study IV-V: Dnr 333-15). For study IV, the Ethical committee at the Erasmus Medical Center in the Netherlands also provided approval (Study IV: ID 2013-293).

Data on patients and controls in Studies IV and V were derived from the Swedish Birth Register, MBR, a national population register. Parents of patients in study IV were approached for inclusion and informed orally and in writing, similar to the study group in the Netherlands. However, individual consent to participate in the study was not regarded as necessary according to the ethics committee. Parents who did not wish to participate were excluded. The studies in this thesis were retrospective, and the children had already undergone CT scans and surgery.

DISCUSSION

The main theme of this thesis is metopic synostosis, and it is divided into surgical results, perinatal outcomes and aetiological aspects. The aims of studies I through III were to objectively evaluate surgical results after correction of MS. Using a population-based national registry, study IV evaluated perinatal outcomes, and study V assessed etiological factors.

Lately, there has been a disparity of opinions regarding the optimal management of MS[91]. The updated guidelines for treatment and management of CS as of 2020 do not recommend surgery in cases of mild MS[92]. At most CF centres, including ours, the maxim has been that treatment of MS involves surgery; however, this maxim is being challenged[93]. The following discussion will move chronologically from aetiology to birth and lastly examine surgical results in the context of this development.

What are the etiological risk factors in craniosynostosis?

Sweden is unique globally in keeping exceptional registry data, which allows for etiological studies. A temporal increase in the incidence of MS has been noted[8] but no cause identified. Known risk factors potentially linked to this increase include maternal age, certain diseases and medications. To evaluate this, we were granted data from the MBR, the inpatients and outpatients register, and the national drug register. To date, we have analysed outcomes using data derived from the MBR in studies IV and V.

In study V we studied parental age, smoking and ART in relation to CS in a large cohort. Since smoking is causally related to foetal growth restriction and other congenital anomalies[94], we included it in the study but found no correlation with CS.

Advanced paternal age is a known risk factor in syndromic CS, as observed in Aperts, Crouzon, and Muenke syndromes. This is due to the paternal age effect that describes the paradoxical selfish selection of certain rare *de novo* point mutations. With age, there is clonal expansion of mutant sperm in males, thereby increasing the risk of congenital anomalies, schizophrenia, and autism[95]. A couple of studies have reported an association of paternal age with NCS. An Australian study demonstrated paternal age as a risk factor for fathers >40 years of age (n = 20), whereas a Danish study showed a positive trend. However, this effect could

depend on the lack of exclusion of syndromic cases[96,97]. This is often the case with data derived from an anomaly registry that does not register suture-specific data, and CS is simply registered under a single ICD code Q75.0. Notably, the GCR is unique in that it registers each synostosis individually. This allowed us to carry out both an overall analysis on the entire CS group and a suture-specific analysis for MS and SS, the two most common forms of NCS.

When studied independently, paternal age was not a risk factor for MS or SS in study V, although maternal age was. Specifically, we found maternal age to be an independent risk factor for CS and SS, and other studies also confirm this relationship[15,98]. Interestingly, we did not find this association in study IV, which might be explained by the larger sample size in study V. Over the decades, advanced maternal age at birth (usually defined as >35 years) has led to an increase in the rate of ART[99]. In our cohort, 40% of CS mothers were >35 years of age compared with 15% of mothers in the control population, with the oldest mother being 59-years old at the time of birth. The risk of having a child with CS increased with age, being the highest in mothers >40 years AOR=1.75; (CI: 1.19-2.59).

Both studies IV and V showed a significantly higher ART rate in children with MS (study V, AOR = 1.79; CI: 1.08–2.98). ART has been linked to a higher risk of congenital anomalies and also to a higher rate of syndromes with epigenetic alterations, such as in imprinting disorders. Imprinting restricts gene expression to one parental allele while the other allele is inactivated, resulting in congenital disorders that affect growth, development and metabolism. Beckwith–Wiedemann syndrome is an example of imprinting disorder with a positive association to IVF[71]. Wilkie et al. (2010) also noted MS after ART and hypothesized that it may be due to the contribution of imprinted genes, although this requires further study[33]. Besides, the underlying cause of subfertility in parents may also be a contributing factor, as noted in males born after ICS. Like their fathers, they too seem to suffer from low sperm count and motility[100].

Foetal constraint theory perseveres but is it worth preserving?

Theories on what causes CS range from the use of crack cocaine to intrauterine compression of the foetal skull. The former is unlikely for many reasons, the most relevant being its lack of confirmation in the literature[101]. However, the latter is a persistent theory often cited as an environmental factor[11,102]. Since the three works by Graham Jr. et al. (1980), FC has received considerable attention[82-84]. They attribute head constraint to early descent, nulliparity, uterine anomalies and breech malpresentation as a cause of CS. Compression of foetal head by

early descent is the mainstay of their argument. Early descent is not an obstetric diagnosis in these works but based on the mother's history of realising if the foetal head dropped. This seems to be elicited on interviews from mothers as late as 16.5 years after giving birth and is found only in 8/16 mothers of children with SS. Yet early descent is cited as the most common cause of SS both in their study[84] and later in their book[85] (Smiths Recognisable pattern of human deformation). Incidentally, in the other eight mothers where early descent did not occur, they noted cephalopelvic disproportion leading to a higher rate of Cesarean section and forceps delivery. Their conclusion was that at least in these cases, SS occurred in early pregnancy and not due to head compression.

That mechanical compression in utero is responsible for deformation, e.g., clubfoot, is well known, but that it can lead to CS in late pregnancy is debatable. Studies claiming causality between mechanical compression and CS are well cited, but given the somewhat subjective nature of their findings, we attempted to systematically study constraint-related factors that were available as variables in the MBR in study V (nulliparity, multiple births and malpresentation). We could not study uterine anomalies as a constraint related factor since they are rare and not listed in the MBR. Since both SS and MS occur in the midline, we postulated that they would be exposed to the same compressional forces and analysed them separately.

Nulliparity as a constraint related factor implies that the previously undistended uterus is less compliant; however, it did not seem to be associated with CS in study V. As we had no triplets or higher birthsin the CS group, we restricted our findings to twins only. The results align with the findings of previous studies, with a higher twin rate of 3.7% in the CS group vs. 2.9% in controls. The multivariate analysis found twins to be a risk factor only for MS and not SS; AOR= 1.98; (CI: 1.11–3.53). This is in line with recent work from Graham Jr et al. (2015), which showed plurality was only increased in MS[12]. Their conclusion, however, was that plurality (and multiple births) might lead to intrauterine constraint in only certain types of CS like MS. We are unable to draw any such conclusions but it is of note that twin pregnancies, in general, are associated with a higher rate of congenital anomalies[103]. This association may also apply to twins and CS.

Malpresentation, especially breech, is often associated with FC[82]. Higginbottom et al. (1980) cited breech as a causative agent of CS in a child with hypotonia and joint contractures who died due to several fractures incurred during the delivery[104]. However, obstetrics studies suggest that breech malpresentation is correlated with low foetal tone as it prevents foetus from achieving a cephalic position[105]. Moreover, it has been shown that breech in itself is a marker for the presence

of congenital anomalies[106]. In study V, we found breech to be more common in CS, MS and SS but only an independent risk factor when we included syndromic cases. We do not think the data supports the belief that breech causes CS, but rather that the inverse is more plausible; that CS is associated with breech.

It is possible that the FC theory perseveres, since no clear genetic cause has been identified in most cases of NCS. FC could not be demonstrated in a sheep model with plate fixation of coronal suture[86], but there is experimental evidence from two studies using small animal models. Koskinen- Moffet et al.[107], did several different experiments, and succeeded in a murine model (unpublished work), which was later repeated by Hunenko et al.[87] (2001). FC was modelled by prolonging gestation in pregnant mice by 2 days through cervical cerclage. Partial, not complete, fusion of the coronal suture with upregulation of FGFR2 and transforming growth factor-β expression were reported[87]. One would thus deduce that mechanical forces trigger synostosis through paracrine signalling. CS induced by mechanical force has previously been demonstrated in an in vitro model[108]. The authors isolated murine calvarial strips with sagittal sutures and applied perpendicular force in a cyclic fashion. This was compared with a control group with no applied load. Cyclic load resulted in histological signs of synostosis. In the FC model, the authors do not mention the use of tocolytics; therefore, one can assume that there are ongoing contractions over a prolonged time. Thus, the skulls of the mouse pups were presumably under the cyclic load of ongoing labour and not the constant pressure of early descent, as posited by Graham et al.[83,84] (1980). Theoretically, it is possible that the FC model is, in fact, an in vivo model of cyclic loading. This may explain why Koskinen- Moffet failed to demonstrate synostosis in another murine model, where amniotic fluid was aspirated[107]. Reducing amniotic fluid mimics crowding better than prolonged gestation, while plate fixation depicts constant compression. Yet both models were unable to induce CS and only showed deformational changes. FC, it seems, is hard to prove or disprove in animal models.

What is the impact of craniosynostosis on perinatal outcomes?

Perinatal complications and higher rates of Caesarean section in children with CS have only recently come to light[2]. At GCC, parents have anecdotally described delivery complications and questioned whether this was related to the abnormal head shape of their child. A similar observation was noted by colleagues at the Erasmus Centre in Rotterdam, which led to the collaboration to study perinatal outcomes (study IV) for the two most common types of CS, SS and MS.

We found a higher rate of medically assisted deliveries in both countries. There was a higher rate of Caesarean section, in particular non-elective Caesarean section. Additionally, study IV revealed different perinatal profiles in the two synostoses. Children with MS had a significantly higher rate of breech, induced labour, and preterm labour. Moreover, children with SS had a higher likelihood of being post-term, having a higher mean birth weight and larger head circumference. Both head shape and size are altered in SS while the compensatory biparietal widening affects the shape in MS. MS children have a higher rate of breech which probably also contributes to the higher rate of Caesarean section. Normal lalour in children with MS and SS seems to be hampered by the altered head shape or size.

Taken together, the increased risk of complicated deliveries in children with SS and MS and lower Apgar scores reported in the literature[68], raise the question of screening for CS. Prenatal detection has previously shown reduced perinatal complications[68]. Prenatal diagnosis of CS is easier on later scans but these are not routinely performed. On the earlier anomaly scan, there is evidence that calculating cephalic index from head measurements would enhance detection of SS[69]. Furthermore, 3D scans allow the visualisation of cranial sutures and skull dysmorphology and may be help to improve perinatal outcomes in the near future.

Is there suitable complication grading for craniofacial surgery?

Study III was designed to identify a surgical grading suitable for CF surgery. Two craniofacial gradings were tested against the surgical gold standard Clavien–Dindo, which is the most widely cited classification system in surgery[89]. The Oxford grading system, though unpublished, has been used for several years by the four main CF centres in England for reporting at audits. We are grateful to Mr. Wall and Mr. Johnson (Oxford Craniofacial Unit) for granting permission to use this classification. It is designed to identify events that could lead to delays in discharge, reoperation, or unexpected long-term deficits, thus covering all relevant aspects of surgery in a simple five-step grading system.

Leeds is not an official CF centre in England, but they have published a comprehensive classification[65]. It divides complications into perioperative, inpatient, and outpatient periods. Unlike the other grading systems, its primary objective is not to identify the most severe complication but rather to detect all events starting at the surgery. Therefore, the Leeds classification detected twice as many complications. We further compared the classifications grade for grade. Leeds and Oxford classifications were in agreement, grading the same complication consistently, whereas Clavien–Dindo did not identify delays in discharge.

The Clavien–Dindo classification is designed for general surgery in adult patients, and we did not find it suitable for the paediatric craniofacial population. The Leeds classification had the disadvantage of being time consuming and thus unsuitable for audits. The Oxford classification appeared to be the best option for established high-volume centres looking for a quality control measure. It already provides a uniform, multicentric comparison of complications in England, and since study III, it is the standard grading system for the two craniofacial centres in Sweden. Comparisons between different CF centres are currently hindered by the lack of a universally adopted system and the Oxford grading could potentially fulfill this role.

Study III also presented a comprehensive review of institutional results at the GCC over 10 years. The complication rate of 13.1% (Oxford) compared favourably with other centres[58,65] (15–36%). We had no mortality during the study period. Complex surgery generally has higher complication rates, as reflected in the midface procedures with a complication rate of 50%. These are lengthy operations (>4 h) accompanied by significant blood loss and usually performed in syndromic children who often have other co-morbidities, such as airway problems. Midface procedures and open cranioplasties were more likely to involve a transfusion of >60 mL/kg. By contrast, this did not occur in the minimally-invasive spring procedures in SS. In MS, the most common complication was impaired wound healing. Furthermore, the revision rate for TH was 7%, with nine corrections during the 10-year period. Interestingly, two of these corrections were on the same patient due to a football-related injury. Four months after correction for temporal retrusion, the child cracked the acrylate by headbutting a football and later required reoperation.

Does surgery for metopic synostosis improve volume?

ICV is often reported in the literature as total volume. Change in the total volume is logical to measure in SS, where the head grows symmetrically. However, in MS, there is compensatory growth in the parietal region and a growth deficit in the frontal region. Since surgery targets volume expansion in the frontal region, the frontal volume or its ratio to the total volume can determine if an effective change is achieved in the desired area. The frontal volume in MS children and age-matched controls was first reported by our centre, with three parameters analysed: frontal volume, total ICV, and the frontal-to-total volume ratio[56]. Total ICV in MS was normal and not reduced, a finding subsequently confirmed by another study[109]. However, the frontal volume was reduced by 30%. After surgery, the frontal-to-total volume ratio improved, but, at long-term follow-up, all three parameters were lower in children with MS than in controls. Therefore, surgery

redistributed the volume but did not normalise it. A possible explanation for this finding could be relapse, and study I aimed to investigate this.

The surgery for MS Children <6 months old involves the insertion of a spring, which is removed half a year later. All operated children undergo routine CT at the 3-year follow-up, but in the MS group, an additional CT is performed at spring removal to ascertain the amount of bone formation. Therefore, we were able to measure the frontal-to-total volume ratio at this intermediate time point and compare it with the volume at the 3-year follow-up. The hypothesis was that if there was a relapse, the volume would be improved at this time point. The results showed that the frontal volume ratio was improved by surgery. However, we observed no significant change in the volume ratio between spring removal and the 3-year follow-up. The conclusion was that the results achieved at surgery pretty much remain. Relapse, at least in the case of volume expansion, does not seem to play a role.

Apart from relapse, other explanations for lack of volume normalisation could be either the age at the time of surgery or an iatrogenic growth inhibition caused by surgery. Surgery in MS is performed early on the growing skull, and thus the ideal age for surgery is often debated. Some centres advocate delayed surgery, arguing that it minimises growth restriction and gives more stable results[18]. However, in our experience, it is not the age at surgery but the extent of the procedure that is a greater determinant of postoperative growth. The two MS cranioplasty techniques are similar in the amount of dissection and osteotomies, but the age at the time of surgery differs. Both groups start with normal ICV before surgery but show reduced volume when compared with controls at the 3-year follow-up. A similar phenomenon of growth restriction is observed in SS children who underwent extensive surgery but not in children operated with minimally-invasive spring technique. Extensive surgery results in minor but significant growth reduction[110].

Does surgery improve appearance?

TH constitutes one of the most common reasons for revision surgery in MS. Across craniofacial centres, the decision for surgery is subjective and based on assessments of photographs. Objective quantification of TH has not been studied; therefore, we designed a MATLAB program for this purpose[111], which was used in study II. Study II showed that surgery only eradicated two-thirds of the deformity despite attempted overcorrection. Before surgery, there was a 3.3% to 3.6% difference (bone transplant and springs, respectively) in the temporal area between cases and controls, which was reduced to 1.1% to 1.0% postoperatively.

Objectve measurement of surgical results in study II indicate that surgery improves the appearance but fails to achieve a fully rounded forehead.

Restoring optimal anatomy with abnormally shaped bone is challenging and may depend on an intrinsic or iatrogenic growth inhibition. The FOA technique requires dissection of the muscle and soft tissues to access the bone. The muscle is repositioned on the advanced bandeau that sits more anterior over a slight bone gap. Contact between bone and dura is lost temporarily, potentially affecting the development of new bone. A recent study supports iatrogenic inhibition. It showed reduced bone thickness in the temporal region after surgery, failure of the temporalis muscle to drape the area and a loss of anatomic position on 3D mapping[112].

To operate, or not to operate?

Traditionally, the most salient reasons to operate NCS stated in literature are cosmetic correction of the deformity, restoring volume, and reducing the risk of elevated ICP and neurodevelopmental impairment[91]. Raised ICP, according to recent evidence, is only present in 1.9% of cases with MS while volume and esthetic results show improvement but a lack of normalisation (studies I and II). The role of surgical intervention in neurodevelopmental outcomes is still debated. It has been suggested that reduced volume may affect cognitive ability due to deformation of the frontal lobes at a critical time during neurodevelopment[40]. However, beyond extrapolation, there is no evidence of either mechanical brain restriction or if surgery mitigates it. Earlier perfusion studies supported this concept by showing lower perfusion in the frontal lobes[113]. This is now refuted by a recent work that quantitatively showed no impairment in cerebral perfusion of the frontal lobe in children with MS[93].

One way to assess the functional benefit of surgery is to compare neurodevelopmental outcomes between operated and unoperated children as attempted by a recent meta-analysis[42]. The findings suggested that unoperated children with MS appeared to perform significantly worse than their normal peers in intellectual functioning, verbal skills, and behavioural issues. They also showed poorer outcomes when compared to the operated children. Findings on operated children vs. normal peers, however, were inconclusive; they showed comparable outcomes but still exhibited difficulties in some domains (attention, motor function etc.) compared to their healthy peers. The meta-analysis was hindered by several limitations, including small sample sizes, lack of control groups, and no socioeconomic background data. This perhaps also highlights that

it is too early to perform a meta-analysis given the lack of adequate comparative data. Based on these findings and from other studies, operated and conservatively managed children seem to show similar results[7,50]. The role of surgery may also be determined by correlating outcomes before and after surgery. One Australian study reported outcomes before and after surgery in NCS, which included fifteen MS children[49]. The authors applied the BSID II, a standardised measure to test motor skills (grasping, etc.) and mental development (jabbering, imitating, etc.) designed to test infants from 1 month of age. The NCS children exhibited lower cognitive and motor scores compared to the normal population before surgery, and even after surgery, the NCS children were more prone to cognitive and motor disability. Thus, neurodevelopmental problems may be part of the underlying mechanism rather than a consequence. However, in most of these studies, we are not comparing like with like. Currently, conservative treatment is usually reserved for mild cases. Thus neurodevelopmental outcomes in unoperated children so far are only reported in those with milder MS. Similarly, children with severe deformities are more likely to be operated on, and it might be that they were on a worse neurocognitive trajectory from the outset.

Preventing abnormal neurodevelopment is one of the main reasons for surgical intervention for 65% of parents[114]. In fact, it is one of the first questions raised by parents we meet. Surgery is only of functional benefit in the cases where it can improve neurodevelopmental outcomes, and this group needs to be better defined through pre-and post-operative testing. Craniofacial surgeons need to address the role of surgery in improving neurodevelopmental outcomes before moving towards a "watch and wait" approach.

CONCLUSIONS

1. The frontal-to-total volume ratio does not change from 6-months post-surgery to 3 years of age, and the low ratio at 3 years of age is thus not due to relapse.
2. Surgery eradicated 2/3 of the initial deformity but did not achieve a fully rounded forehead as seen in controls.
3. The Oxford classification is suitable for grading complications in CF surgery.
4. SS and MS exhibit two different perinatal profiles, and both SS and MS children have a higher rate of complicated births. A higher rate of ART appears to be associated with MS.
5. Maternal age, twins and ART are independent risk factors for MS; however, neither nulliparity nor breech were risk factors for MS or SS, indicating that foetal constraint is not an etiological factor in CS.

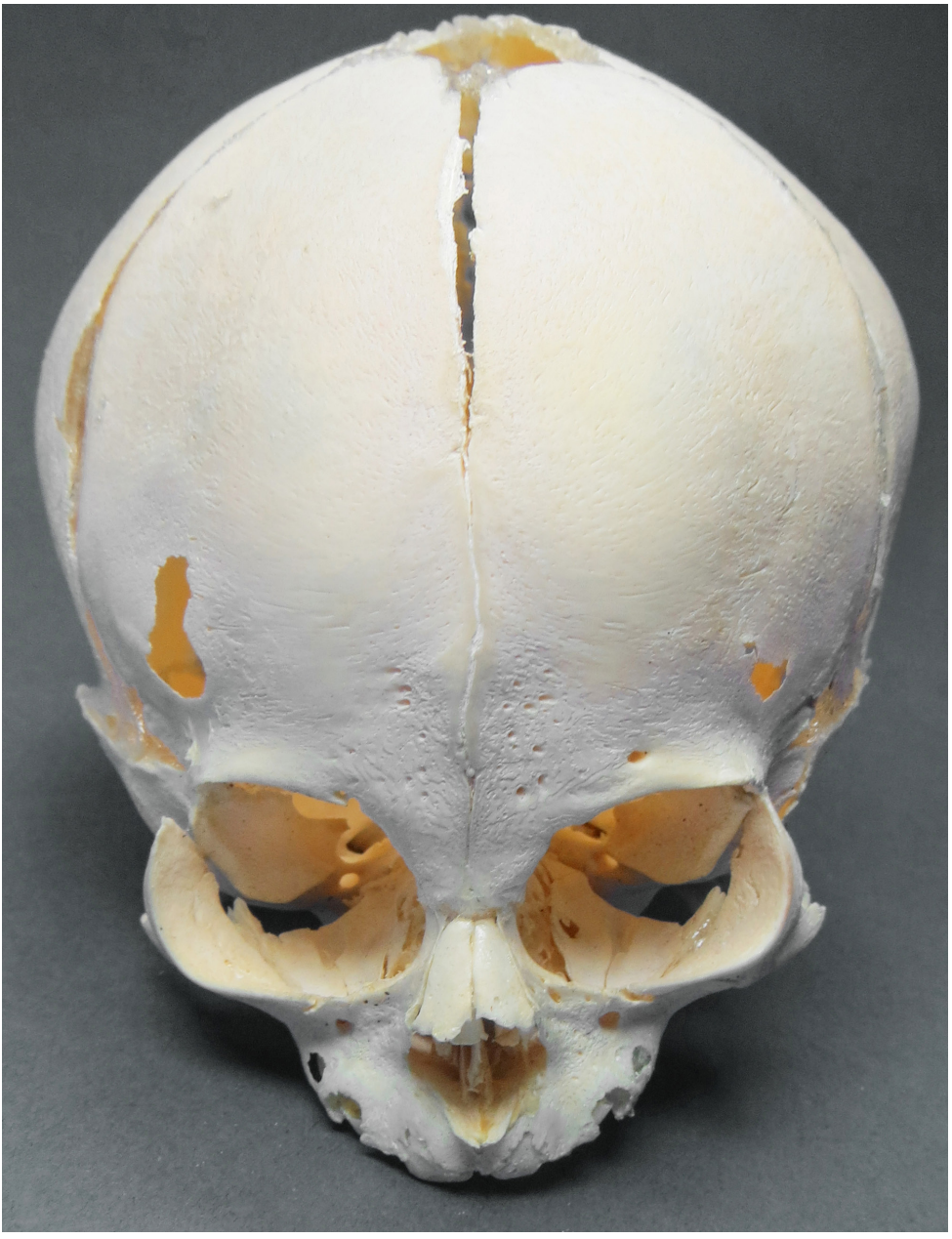

Figure 13: Foetal skull with partially fused metopic suture. Formerly on display at the Wellcome Museum of Anatomy and Pathology. By permission from the Royal College of surgeons.

FUTURE PERSPECTIVES

We plan to continue investigating etiological factors for CS and work with available registry data from the drug register, and patients register to delineate potential association with medications or maternal diagnoses. Furthermore, an ultrasound study in monozygotic twins would clarify the role of head constraint. Additionally, we hope to study the role of different ART techniques in children with CS through the Q-IVF register.

The genome-wide association study has recently identified BMP7 loci as a risk factor for MS[115]. Simultaneously rapamycin has been shown to rescue BMP-mediated CS in a murine model[116]. Further research in this field may provide answers to aetiology and perhaps even medical treatment of CS in the future.

Moving forward, objective criteria for surgical intervention need to be defined. The European guidelines currently recommend conservative treatment for milder cases; however, all trigonocephaly is not created equal; thus, an objective measure of severity is necessary. Moreover, the overall functional benefit of surgery needs to be evaluated by comparing neurodevelopmental outcomes before and after surgery. This could be accomplished in a matched longitudinal study comparing operated and unoperated children of equal severity with the normal population. Several validated tools to grade severity, such as interfrontal angles, maybe applied[117]. Pre- and postoperative neurodevelopmental and non invasive ICP outcomes could be followed with standardised testing in the surgical group beyond school age. Assessments of quality of life and psychosocial follow-up on how unoperated and operated children feel about their appearance would also be interesting, as these areas are not well studied. Reports on endoscopic surgery claim minimal growth inhibition and shorter operation times[52,118]. The envelope could be pushed further by including an endoscopic arm to clarify what part is played by the burden of surgery.

Given the relative rarity of MS as a diagnosis, individual centres are unlikely to produce adequately powered studies. Thus, only multicentre research is likely to generate enough data for the necessary statistical power to provide conclusive evidence for or against surgical intervention.

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