The Utilisation of Craniomaxillofacial Radiology in Preventative Medicine.

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A thesis submitted to the University of Adelaide in fulfillment of the requirements of the Degree of Doctor of Philosophy.

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Abstract

This thesis discusses the importance of the maximal utilisation of dental, maxillofacial and antenatal craniofacial imaging in preventative healthcare. Many craniomaxillofacial imaging techniques can provide added diagnostic information which assist in the diagnosis of conditions other than those that the study was performed to investigate. The first publication describes use of panoramic dental radiographs in the assessment of stroke risk in the individual patient. The second publication discusses the uses and limitations of panoramic dental radiographs in the evaluation of maxillary sinus disease. The final three articles establish the normal fetal cephalic index, and its value in the antenatal detection of sagittal craniosynostosis.

The results of these studies will assist dental and medical professionals in the appropriate investigation and management of patients with carotid artery calcification detected incidentally on orthopantomograms, and the selection of the most suitable imaging studies to evaluate the maxillary sinuses. The antenatal diagnosis of sagittal craniosynostosis can provide valuable information to the expectant mother and her obstetrician with regards to delivery options and choices where there is an increased risk of obstructed labour that could injure mother, child or both. The full utilisation of these imaging studies will provide an increased clinical benefit to the patient and referrer, and can benefit the population as a whole by assisting with preserving the health of the community and managing spiralling healthcare costs.

Declaration

I, Sarah Christine Constantine, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed

Sarah Christine Constantine

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Finally, my sincere gratitude to Professor David David for inspiring me to research the area of craniosynostosis in the antenatal period, and Professor John Beltrame for his encouragement to undertake a Doctor of Philosophy degree.

Dedication

This thesis is dedicated to my maternal grandfather.

"*Boys will find their own way in life, but you must educate your girls. You are then educating the next generation*" Sir Fred Drew, 1895 – 1986.

Chapter One

Introduction

Chapter One

Introduction

"In the first Place, as an Ounce of Prevention is worth a Pound of Cure,…". When Benjamin Franklin wrote these words, published in The Pennsylvania Gazette in 1735[1], he was referring to the prevention of fires in Philadelphia, after comparing local events to his home town of Boston. In the intervening centuries, "prevention is better than cure" has become a well-known and frequently used metaphor. It is unlikely that is was immediately translated to use in healthcare, with the background of 18th century medicine that had almost no cures – there was little anaesthesia, no antibiotics, and minimal antisepsis. The then available "treatments" were often more likely to kill than the illness itself. But as healthcare began to improve, and both the fields of prevention and treatment developed, the validity of the metaphor became more evident.

The Oxford English Dictionary defines "cure" as "To heal, restore to health (a sick person of a disease)"[2]. This does not necessarily indicate that the "cured" individual will be as they were prior to the illness. Many infectious diseases, largely in the past, could be survived, the patient healed and restored to health, but left with the terrible sequelae of the active infection. Examples include smallpox, which left the survivor severely scarred, and poliomyelitis which left many of its victims paralysed to varying degrees. Today the community fears meningococcal sepsis, which is highly lethal, and leaves the majority of its survivors with amputations as the result of gangrene. Clearly, in diseases such as these, prevention is far preferable to any cure.

The Oxford English Dictionary defines "prevention" as "The action of keeping from happening or making impossible an anticipated event or intended act"[3] and "prevent" as "To anticipate or act in advance"[4]. This has many applications in preventative healthcare, as attempts are made to prevent illness and injury, as well as the complications associated with the treatments or cures. Prevention has many different methods and approaches. Society can actively and deliberately attempt to prevent illness and preserve health with vaccination, screening programs, fortification of food and water with vitamins and minerals, legislate the compulsory use of seatbelts in vehicles and the wearing of helmets while cycling. Education plays a strong role in prevention, including teaching children to look both ways for traffic before crossing the street, advocating the importance of an active healthy lifestyle, the cessation of smoking and the prevention of obesity. Prevention can also be a beneficial "side-effect" of our modern healthcare system. Salicylic acid, commonly known as aspirin (Bayer, registered tradename), was developed as an analgesic[5], but its major use today is as an anticoagulant, and there is growing evidence it can assist in the prevention/treatment of some cancers[6-8]. But there is also a negative side to prevention in healthcare which is often neglected. The overuse of antibiotics has led to the development of multi-resistant organisms or "super-bugs" that cannot be treated[9-11]. The increasing use of medical imaging, an essential in modern medical diagnosis, is purported to be the cause of 1-2% of all cancers in humans[12, 13].

There is little doubt that many preventative healthcare strategies have been a massive success, both in the health of the community and the financial benefit to the healthcare system. One example is the addition of fluoride to the water supply for the prevention of dental caries. The benefits of fluoride on dental health were first

recognised in the early 20th century. Water fluoridation began in Michigan, USA in 1945[14], and fluoride began to be added to the Australian water supply in Tasmania in 1953[15]. The proportion of the Australian population that now receives fluoridated drinking water varies from 70% in the Northern Territory to 100% in the Australian Capital Territory[15]. The National average is that 89% of all Australians receive fluoridated water[16]. Water fluoridation reduces dental caries by 26 – 44% in children and adolescents[15]. In 1999, the Centers for Disease Control and Prevention in the USA recognised water fluoridation as one of the ten greatest public Health achievements in the twentieth century[17]. A recent paper estimated the annual cost of water fluoridation in urban areas of Australia to be twenty six cents per person[16]. While the cost is substantially higher in rural areas (estimated at twenty six dollars per person per year)[16], there is no doubt that this is significantly less than the cost of even a single dental restoration. The conclusion of this and several other studies is that the fluoridation of water is extremely cost effective in the prevention of dental caries[16-19]. Water is a commodity that the entire community utilizes, so the fluoridation of water reaches very large sections of the population. This is an essential component of any preventative healthcare program.

Given the improvements in healthcare, it could be expected that the population will be robustly healthy and long-lived, with all these preventive healthcare measures available and affordable to all. Despite these, it is now becoming evident that a child may not live as long as its parents, nor be as healthy as their parents were. Western society has been successful at combatting malnutrition, childhood infection and premature death from injury, but new health problems have arisen that may be as problematic as the afflictions they replace. Around one quarter of children and two

third of adults in Australia are now overweight[20], with an increasing risk of hypertension, hypercholesterolaemia, diabetes and osteoarthritis, all of which are associated with earlier mortality, especially from cardiovascular events. Even in healthy people a longer life increases the likelihood of developing chronic disease such as arthritis, cardiovascular disease, dementia and malignancy. Two further issues that are very modern healthcare problems: the use of illicit drugs and the overuse of ionising radiation, both of which are likely to impact upon the population health in the coming years[12, 13, 21, 22]. Western society has been supremely successful in eliminating a number of serious health conditions that affected the population for many centuries, but in doing so have allowed the prevalence of other previously unknown or rare conditions to flourish. However, one of the biggest problems created is the monumental costs of managing these chronic diseases of older age and their sequelae[23-25].

Another facet of prevention in healthcare relates to the costs associated with providing that care. Healthcare is focussed on providing treatments rather than cures for many of our 21st century first world diseases such as diabetes, heart disease, arthritis, obesity and dental disease. The ongoing costs of treatment for these are substantial, and the health system is struggling to manage these costs[26]. As healthcare develops, it may well be that the most significant area of prevention becomes preventing the inappropriate overuse of healthcare and controlling healthcare expenditure. At the beginning of the 20th century, a patient with a suspected cerebral haemorrhage might have had a skull x-ray, but was largely treated on the basis of clinical signs and symptoms. By the 1980s, CT scanning was available, and the patient would receive a diagnostic or pre-operative CT scan to assist clinical

diagnosis. By the 1990s, MRI scanning was often performed as well, and multiple post-operative follow-up CT scans are also performed. The question can be asked: "Has the clinical outcome for the patient improved in the last century, allowing for the advances in anaesthesia, surgery, antisepsis and nursing care?" What is the optimal intervention for care? What harm is potentially being caused with the additional radiation from so many scans, and is the cost justified?

The increase in utilisation of diagnostic imaging has continued throughout the 1990s and early 21st century[27, 28]. Between 1997 and 2006, CT scanning increased by 14% in the United States of America (USA), with costs of cross sectional imaging increasing from 54% of total imaging costs to 70% over the same time period[29]. Since CT scanning became readily available in 1980, the number of scans in the USA has increased from 3 million annually to over 60 million annually in 2005[30], with similar increases in other countries including Australia[31, 32]. In the last 10 years growth in imaging has slowed, but less so with CT than MRI, which does not use ionising radiation, and therefore does not have the same cancer risks. The CT growth rate reduced from 10% in 1998 - 2005 to 5% in 2005 - 8[27]. Imaging from emergency departments, however, is continuing to increase[33]. It seems the over-requesting of high radiation dose imaging is widespread, with over 85% of emergency physicians believing too many diagnostic tests are being ordered, and 97% admitting to ordering unnecessary imaging tests[34]. "Wasteful healthcare" was estimated at a cost of US$750 billion in 2009[35], a figure that cannot take into account the costs associated with any cancers caused by this over-imaging. If 1-2% of cancers are attributable to medical imaging[12], this figure could be substantial.

Should society refocus preventative efforts to both prevent disease and the chronic sequelae of disease, as well as control the costs associated with both the prevention and management of disease in the population? Resources ought to be used appropriately, both to ensure there is no financial wastage, but also the prevent over-servicing which can have long term adverse consequences when, for example, the use of medications and ionising radiation is involved. One method of achieving both these goals is to have use of all the diagnostic information gained from any radiological investigation. Almost all imaging will involve some coverage of an area or organ not specifically required by the clinical reason for performing the investigation. Radiologists are trained to peruse all areas of the image, but the information may need to be interpreted in a slightly different manner from the conventional method, ensuring that any and all investigations are appropriate for the diagnostic information required.

A recent report by the Australian Institute of Health and Welfare found that health expenditure increased from 6.5% of gross domestic product (GDP) in 1989/90 to 9.7% of GDP in 2013/14[23] It was noted that this is faster than the rate of inflation, and faster than the rate of population growth and population ageing. Figure 1, taken from that report, clearly shows the rate at which health expenditure is increasing[23]. The per person expenditure increased by almost 125% over the past 25 years, and with an ageing population this is likely to accelerate. It seems obvious that it not sustainable for healthcare costs to continue to increase at this rate indefinitely; the country simply cannot afford it.

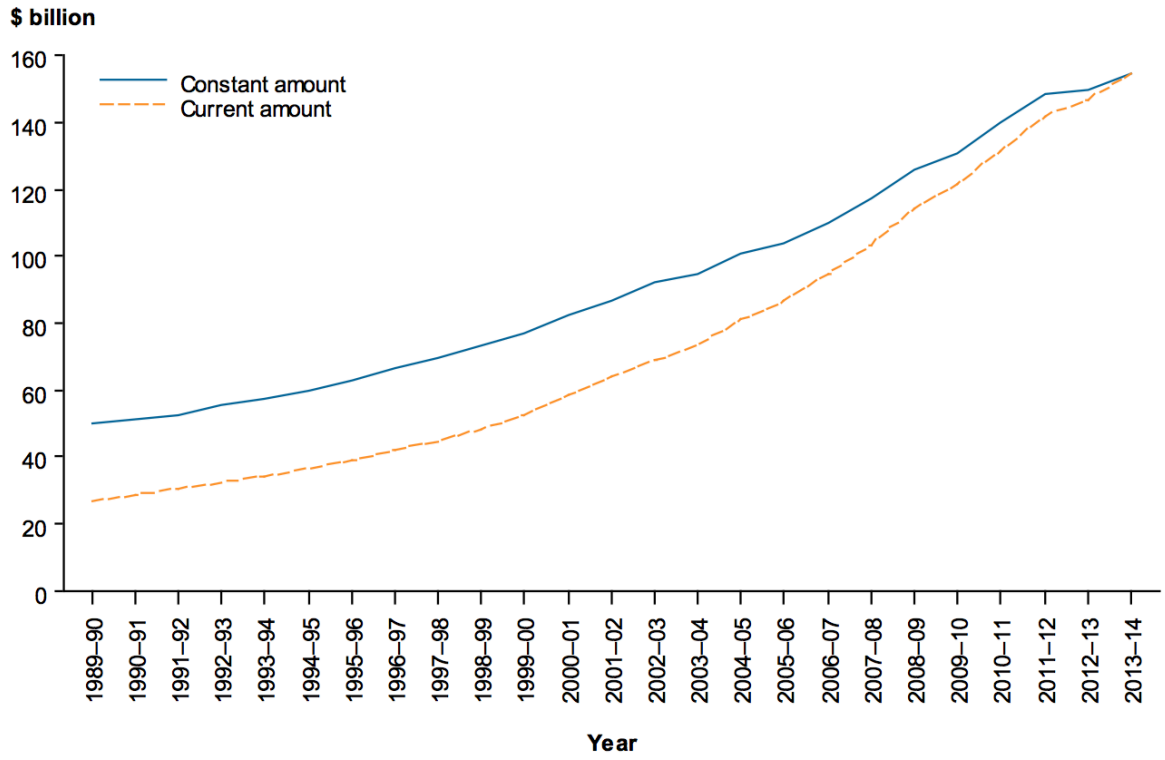

Figure 1. Total expenditure on health, current and constant prices, 1989/90 to 2013/14. Taken from Australian Institute of Health and Welfare 2016. 25 years of health expenditure in Australia 1989–90 to 2013–14. Health and welfare expenditure series no. 56. Cat. no. HWE 66. Canberra: AIHW .

In the 21st century, it seems an ounce of prevention could well be worth millions of dollars of cure, but the cost of prevention must also be kept under review. The benefits to the wider community, both in health and financial health, have long been recognised for our current cancer screening programs[36, 37], vaccination programs[38, 39] and fortification of drinking water with fluoride[15, 17], flour with thiamine[40, 41] and dairy products with vitamin D[42, 43]. Other methods of prevention need to be adopted to keep the population as healthy as possible while minimising cost to the taxpayer. One strategy to do this involves the utilisation of diagnostic tests in the prevention of other diseases. This is not a new concept, but one that need to be expanded if the country is to try and control the spiralling healthcare costs. Efforts have been made

in the past, and are still being published in the current literature, to use diagnostic imaging tests for multiple purposes. For example, there is quite a lot of literature based on the possibility of diagnosing osteoporosis from orthopantomograms (OPGs)[44-50].

The following published articles show examples of how diagnostic imaging tests can be used to detect patients at risk of significant health compromise using imaging features aside from the area of clinical concern, and with minimal extra financial cost, can prevent a significant health burden both to the individual, and the health care system. These studies are focussing specifically on craniomaxillofacial and obstetric ultrasound imaging used for diagnostic purposes, and how other health conditions can potentially be identified and addressed at the same time. OPGs performed for dental diagnostic purposes may be used to assess the risk of stroke (publication 1). Radiation dose can be modulated by utilising the best diagnostic test for sinus disease, that CT scanning rather than OPG (publication 2). Damage to the maternal pelvic floor/perineum and complications of obstructed labour may be avoided if sagittal craniosynostosis is identified antenatally, leading to an appropriate delivery plan if labour fails to progress as expected (publications 3 – 5). All of these preventative measures can both improve the patient's health, as well as being cost effective in our health system.

Chapter Two

Panoramic dental x-rays and the risk of stroke

Statement of Authorship

Title of Paper	Carotid Artery Calcification on Orthopantomograms (CACO Study) – is it indicative of carotid stenosis?
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Sarah Constantine
Contribution to the Paper	• Original study concept • Study design • Reporting of all panoramic xrays • Patient consents • Data collection and interpretation • Preparation of final paper
Overall percentage (%)	50%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 15/5/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Denise Roach
Contribution to the Paper	• original study concept • reporting of all ultrasound scans • patient consents • preparation of final paper
Signature	Date 12·6·19

Name of Co-Author	A/Prof Sharon Liberali
Contribution to the Paper	• patient recruitment • preparation of final paper
Signature	Date 16.5.19

Name of Co-Author	Dr Andreas Kiermeier
Contribution to the Paper	• statistical analysis • preparation of final paper
Signature	Date 16 May 2019

Name of Co-Author Dr Paroma Sarkar

Contribution to the Paper

• patient recruitment and consent
• preparation of final paper

Signature Date 10/06/2019

Name of Co-Author	A/Prof Jim Jannes
Contribution to the Paper	• original study concept and design • preparation of final paper
Signature	Date 22nd May 2019

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Contribution to the Paper	• study design • final paper preparation
Signature	Date 10th June 2019

Name of Co-Author	Professor Peter Anderson
Contribution to the Paper	• data interpretation • preparation of final paper
Signature	Date 28/6/2019

Name of Co-Author	Professor John Beltrame
Contribution to the Paper	• original study concept • study design • interpretation of results • final paper preparation
Signature	Date 22/5/2019

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Carotid Artery Calcification on Orthopantomograms (CACO Study) – is it indicative of carotid stenosis?

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ABSTRACT

It is unclear whether incidental carotid artery calcification (CAC) on radiographs has a defined relationship to clinically significant carotid artery stenosis, and therefore risk of stroke. The primary objective of this study was to ascertain the relationship between dental radiograph detected carotid calcification and carotid artery stenoses ≥50% on carotid duplex ultrasound. We carried out an observational study of patients undergoing routine dental orthopantomogram (OPG) examinations. Consecutive patients with CAC on OPG were prospectively matched to those without CAC based on age and gender. Ultrasound of the carotid arteries was performed to determine the presence of stenosis (≥50%) in either vessel. Of 5780 consecutive OPG examinations with suitable images for analysis, CAC was detected in 10.8%. A total of 233 patients underwent carotid ultrasound (130 with and 103 without CAC on OPG). The prevalence of a clinically significant (≥50%) carotid stenosis on ultrasound was 15.4% (20/130) in those with CAC and 5.8% (6/103) for those without CAC on OPG. Incidental CAC detected on routine OPG requires both radiological reporting and clinical follow-up since 1 in 7 patients will have a clinically significant carotid artery stenosis as compared with 1 in 20 patients who do not have CAC.

Trial Registration: Australian and New Zealand Clinical Trials Registry website (U1111-1148-1066). http://www.ANZCTR.org.au/ACTRN12613001038785.aspx

Keywords: Carotid stenosis, doppler, duplex, incidental findings, panoramic, population health, radiography, ultrasonography.

Abbreviations and acronyms: OPG = orthopantomogram; CAC = carotid artery calcification; TIA = transient ischaemic attack; IHD = ischaemic heart disease; PPV = positive predictive value; NPV = negative predictive value; SD = standard deviation; CI = confidence interval.

(Accepted for publication 7 September 2018.)

INTRODUCTION

Orthopantomograms (OPGs) are often performed in the diagnosis and management of dental disease. Incidental carotid artery calcification is frequently observed in OPG examination[1–11] but its clinical relevance is uncertain, especially in the context of an asymptomatic patient undergoing dental evaluation. Specifically, it is unclear whether these incidental carotid artery calcifications on routine dental panoramic radiographs are indicative of a clinically significant carotid artery stenosis and therefore warrant further assessment.

Previous studies evaluating the relationship between carotid artery calcification on OPG and a significant carotid stenosis[5,8] have been inconclusive. Thus, the evidence-base to advise referrers on the appropriate management of patients with these incidental findings is ambiguous, often resulting in conflicting recommendations. Several studies recommended referral of affected patients for further carotid artery investigations,[6–11] which

is potentially a significant financial burden upon the health system, without a proven population health benefit.

To evaluate the clinical relevance of incidental carotid artery calcification on OPG is to establish if the calcification is indicative of a significant carotid stenosis. The primary objective of this study was to ascertain the relationship, if any, between dental radiograph detected carotid artery calcification and carotid artery stenoses ≥50% on carotid duplex ultrasound, taking into account potential risk factors.

MATERIALS AND METHODS

To achieve the above objectives, a study was undertaken of consecutive patients undergoing OPG examinations for dental indications. The Queen Elizabeth Hospital/University of Adelaide Human Research Ethics Committees approved the study.

OPG studies – patients screening

From March 2012 to March 2014, all OPGs undertaken at the following dental/radiological practices were screened for carotid artery calcification: (i) the South Australian Dental Service – a government-funded public dental service, (ii) InCiDental Imaging – a private specialist dental imaging practice in Adelaide, and (iii) Benson Radiology – a general radiology practice in the Western suburbs of Adelaide, South Australia. This dental imaging network represents 8.3% of radiologically assessed OPGs (Medicare Data, Australian Government, Department of Health) performed in the state of South Australia, which has a population of 1.67 million.[12]

All OPGs were performed by qualified radiographers using industry standard techniques to obtain high-quality images (Fig. 1). Patient size and oral health status were used to determine the radiologic exposure factors, with the average image requiring 68 kV at 9 mA with a 14 s rotation time. The equipment used is listed in Table 1.

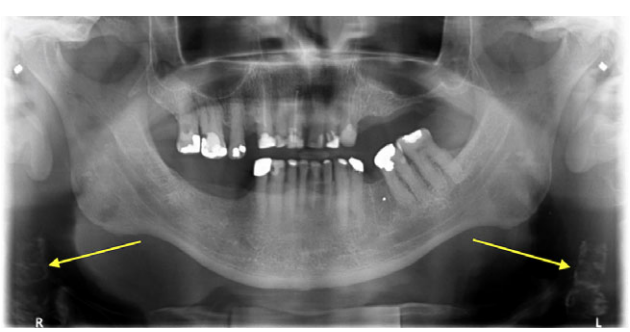

Fig. 1 Orthopantomogram showing bilateral carotid artery calcification (arrows).

Table 1. Machines used in the production of the panoramic radiographs

SA Dental Service	Carestream	CS9000
InCiDental Imaging	Vatech	PaX-Reve3D
Benson Radiology	GE Instrumentarium	OC100D

Patient selection

The panoramic images of dental patients were screened for the presence of carotid artery calcification on either side of the neck by a radiologist with significant dental imaging experience, who was blinded to the patient's cerebrovascular history (SC). Patients were assigned as study patients (CAC positive group) or 'controls' (CAC negative group) based on the presence/absence of carotid artery calcification on the panoramic image. The presence of carotid artery calcification (CAC positive group) was defined by the following inclusion criteria: (i) a linear or mass-like vascular calcification adjacent to the cervical vertebrae, that (ii) occurs at the level of the third or fourth cervical vertebrae. A patient was allocated to the CAC positive group if the carotid artery calcification was evident unilaterally or bilaterally. Exclusion criteria included: (i) age <18 years, (ii) inadequate views of the pre-cervical region – not uncommon considering these are dental images, (iii) previous carotid artery revascularisation (surgery or stenting), (iv) previous radical neck dissection for malignancy, or (v) symptoms suggestive of transient ischaemic attacks. Radiographs where there was such a small amount of calcification that it could not be confirmed as being vascular were considered to be CAC negative.

Following identification of a patient with carotid artery calcification on panoramic image, the next sequential screened patient fulfilling the following criteria, was assigned as a 'matched control' (CAC negative group): (i) absence of carotid artery calcification, (ii) age within 5 years of the study patient, (iii) same sex as the study patient, and (iv) absence of the above exclusion criteria (Fig. 2).

Carotid artery ultrasound

Patients selected as CAC positive and CAC negative, were contacted and invited to undergo a carotid artery ultrasound. All carotid ultrasound scans were performed at The Queen Elizabeth Hospital by one of three sonographers trained and experienced in vascular ultrasound. All patients were scanned with a Philips IU22® (Philips Medical Systems, Bothell, Washington, USA) ultrasound machine using a linear 9-3MegaHertz probe with carotid presets. The ultrasound scans were reported by a vascular surgeon with ultrasound certification and experience (DR). The participants, the sonographers and the vascular sonologist were all blinded as to presence/absence of carotid artery calcification on

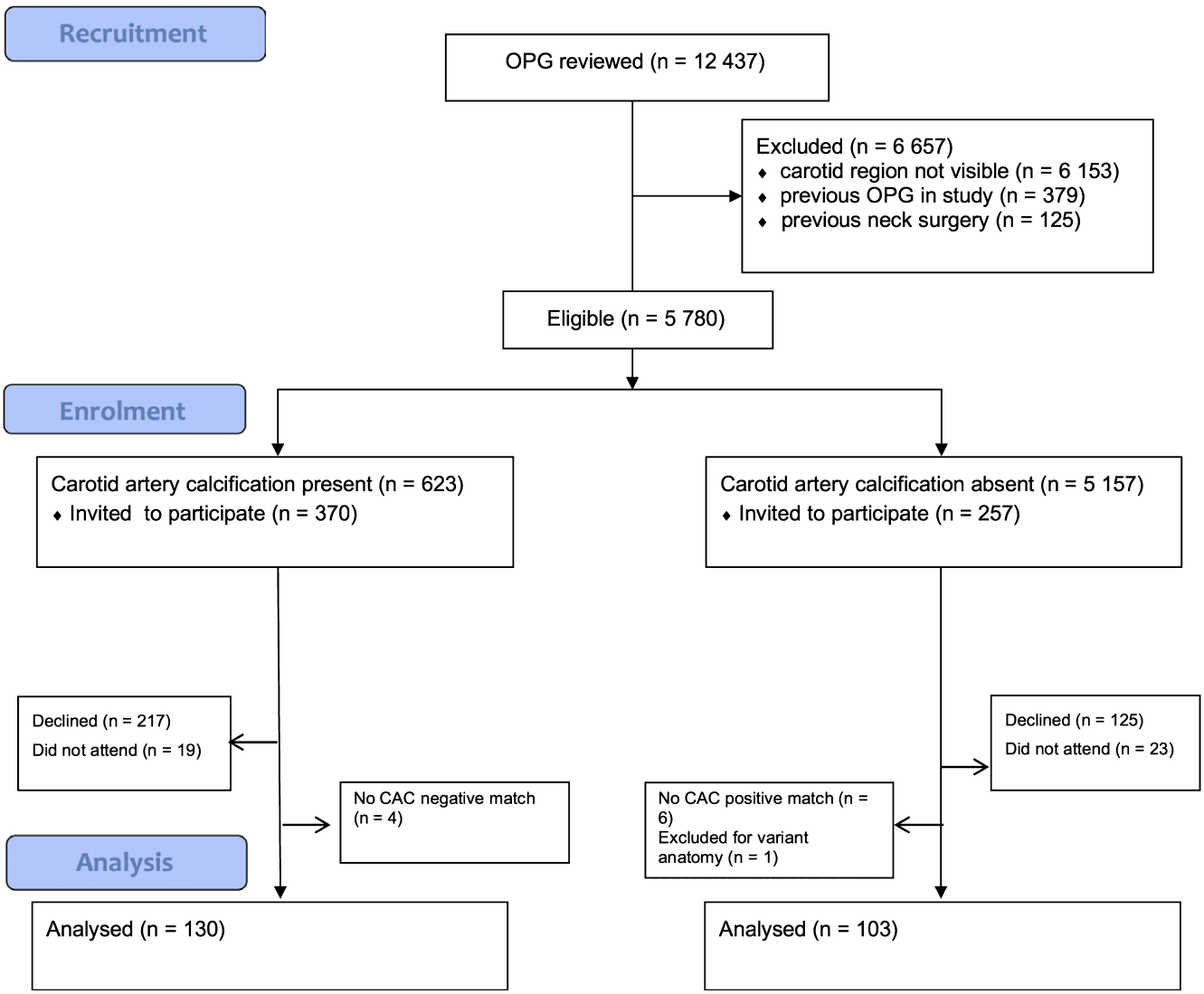

Fig. 2 CONSORT diagram of patient enrolment into the CACO Study.

the participant's OPG. All patients were scanned within 2 months of the OPG being performed and both sides of the neck were scanned.

Carotid stenosis severity was determined by assessment of the velocity changes in segments of the carotid artery as per established guidelines (http://www.asum.com.au/files/public/SoP/D14-Duplex-Ultrasound-Extracranial-Carotid-Artery-Disease.pdf). A clinically significant carotid stenosis was defined as a lesion ≥50% in either carotid artery, with notation made as to which artery was affected. The carotid artery ultrasound report detailed the extent of internal carotid artery stenosis based on criteria endorsed by the Australasian Society for Ultrasound in Medicine.

Data collection and study endpoints

Clinical information, including patient age, sex, vascular risk factors (smoking status, hypertension, diabetes, cholesterol status, family history), prior history of cardiovascular disease (coronary, cerebrovascular, and peripheral vascular disease), current medications, and TIA symptoms were collected for all study patients and based upon self-report. Radiological details of the OPG and carotid ultrasound were also documented for each patient including the site of carotid calcification as well as the site and extent of any carotid artery stenoses on ultrasound examination.

The primary endpoint for this study was the presence of a carotid stenosis ≥50% detected on carotid ultrasound in either internal carotid artery. This endpoint was chosen on clinical rationale, with a stenosis of <50% being considered clinically insignificant and not requiring further follow-up, whereas a stenosis ≥50% having a significant risk of stroke, necessitating clinical follow-up.[13,14]

Data analysis

A sample size calculation was determined based on the findings of Yoon *et al.*,[7] where the sensitivity and specificity of panoramic image carotid calcification to detect a significant carotid stenosis was 22% and 90%, respectively, with a prevalence of 0.02. Thus, to assess the primary endpoint in this study, a minimum of 99 patients in each group were required for 95% confidence intervals.

All data analyses were carried out in the open-source, statistical software R (version 3.4.0).[15] A binary mixed effect model was fitted to data – the binary response was ≥50% stenosis, and explanatory variables (fixed effects) collectively considered in the model (no interactions) included CAC status (positive/negative) and all clinical information collected as part of the self-reported questionnaire and excluding age and gender which were used for matching. Matched pairs/clusters were incorporated as random effects in the model.

RESULTS

Prevalence of carotid artery calcification on OPG

Of the 12,437 dental patients who had an OPG performed, 6,153 patients were excluded because of limited field imaging on the OPG (Fig. 2). A further 379 individuals were excluded for repeat imaging (previous OPG already included) and 125 were excluded due to previous neck dissection/carotid artery revascularisation. Of the remaining 5,780 patients with adequate views, carotid artery calcification was observed in 623 patients reflecting a patient prevalence of carotid artery calcification in dental patients undergoing an OPG of 10.8%.

Carotid artery stenosis on vascular ultrasound

Patients with adequate OPG images to detect carotid calcification were progressively contacted following their OPG examination. Of the 623 patients with carotid artery calcification, 370 consecutive patients were invited to undergo a carotid ultrasound study of which 134 patients (36%) accepted the invitation and completed the scan. Of the 5,157 patients without evidence of carotid calcification on OPG, 257 patients were selected as age and sex matched controls and invited to undergo a carotid ultrasound study. Of these 110 patients (43%) accepted the invitation for a carotid ultrasound study and completed the scan.

The reasons for declining an ultrasound were similar in both groups, and included lack of interest in the study, working and no time to attend, and no transport to the hospital. A number of potential participants were also not contactable by telephone (three attempts were made) and several others consented to participate but did not attend for the ultrasound.

The clinical characteristics of the 233 patients who underwent carotid ultrasound are summarized in Table 2. Ten patients were excluded after scanning due to lack of a 'match' of the same gender and age (Fig. 2). One patient was excluded due to variant anatomy (no common carotid artery with the internal and external carotid arteries arising directly from the aortic arch). Consistent with the study design, the groups were closely matched for age and sex, but patients with carotid artery calcification were more likely to have diabetes, hypercholesterolaemia, and a history of ischaemic heart disease compared to controls.

Carotid ultrasound examination revealed significant stenoses (≥50%) in 26 study patients (11.2%), of which 20 and 6 were in the CAC positive and CAC negative group, respectively. A total of five patients in the CAC positive group had bilateral carotid stenoses. Ignoring all other explanatory variables, the sensitivity and specificity of carotid artery calcification on OPG for identifying significant carotid stenosis on vascular ultrasound were 76.9% (95% CI: 60.7, 93.1%) and 46.9% (40.1, 53.7%), respectively (Table 3). Thus, the positive predictive value (PPV) of carotid artery calcification on OPG for predicting carotid narrowing was 15.4%, and the negative predictive value (NPV) was 94.2%.

To determine if the presence of CAC on OPG was an independent clinical predictor of carotid stenosis, a regression analysis was undertaken with the model results summarized in Table 4. The only statistically significant predictor of ≥50% stenosis was hypertension, with an estimated odds ratio of 5.0 for patients with hypertension compared with those without. While none of the other predictors were statistically significant, CAC on the orthopantomogram, use of anticoagulant medication and current smoker status ranked second to fourth most significant (P-values of 0.108, 0.111 and 0.118).

Table 2. Clinical characteristics of patients enroled in the CACO study

Clinical feature	CAC positive (n = 130)	CAC negative (n = 103)
Age in years (SD)	69.2 (9.2)	69.2 (9.3)
Male	43.8%	47.6%
Current smoker	15.4%	9.8%
Ex-smoker	19.2%	13.7%
Hypertension	60.0%	49.0%
Diabetes	15.4%	4.9%
Hypercholesterolaemia	59.2%	42.2%
Ischaemic heart disease	12.3%	2.0%
Cerebrovascular disease	6.9%	5.9%
Peripheral arterial disease	4.6%	1.0%

Table 3. Carotid artery calcification vs. carotid stenosis

	Carotid stenosis ≥50% on ultrasound	Carotid stenosis <50% on ultrasound	Totals
Carotid calcification on OPG	20	110	130
No carotid calcification on OPG	6	97	103
Totals	26	207	233

DISCUSSION

To our knowledge, this is the first study examining the significance of carotid artery calcification, utilizing matched control patients (CAC negative) as well as study patients (CAC positive). This prospectively designed observational study of consecutive dental patients undergoing OPG, demonstrates an estimated prevalence of carotid calcification of approximately 11% of panoramic images. When carotid calcification is demonstrated on OPG, the probability of detecting a clinically significant (≥50%) stenosis on vascular ultrasound is 15%, representing a threefold higher risk of a significant lesion than those without calcification. Thus, for every seven patients with carotid calcification on OPG, one is expected to have a clinically significant carotid artery stenosis on vascular ultrasound, compared to about one in twenty without CAC on the OPG. These findings suggest that incidental carotid artery calcification noted on OPG warrants further clinical evaluation.

Previous carotid artery calcification studies

Consistent with our study, previous investigations have reported a low efficacy of carotid artery calcification for predicting significant carotid artery narrowing.[7,8,11,16] However, few studies have carried out a cohort study with prospective allocation of age and sex-matched control patients. Studies that have not identified a relationship between carotid artery calcification and carotid stenosis[1,2] might be underpowered considering the low prevalence of carotid calcification. Furthermore, the operator-dependent technique for identifying carotid disease on ultrasound is dependent upon the experience of the sonographer.

Table 4. Estimated odds ratios for all predictor variables (presence/yes vs. absence/no) included in the model, including 95% confidence intervals and P-values

	Odds ratio	95% CI	P-value
Smoker	12.74	0.52, 310.02	0.118
Ex-smoker	0.22	0.01, 4.17	0.314
Hypertension	5.00	1.14, 21.87	0.033
Diabetes	1.28	0.33, 4.92	0.724
Hypercholesterolaemia	0.64	0.15, 2.76	0.552
Ischaemic heart disease	2.22	0.53, 9.25	0.275
Stroke	0.60	0.10, 3.45	0.563
Peripheral vascular disease	1.04	0.13, 7.97	0.973
Angina	1.12	0.22, 5.59	0.892
Family history of IHD	0.79	0.30, 2.05	0.625
Family history of stroke	0.43	0.13, 1.36	0.150
CAC on OPG	2.40	0.83, 6.99	0.108

Clinical implications

The study findings have important clinical implications for radiologists, dentists, and general practitioners. Although dental radiographs were first used soon after Wilhelm Röentgen's discovery of x-rays,[17] the reporting of dental x-rays amongst general radiologists is often considered 'routine' and the presence/absence of carotid calcification on OPG might often be neglected.[18] Previously the clinical relevance of reporting carotid calcification was unclear so that its necessity was unjustified. Although we have not shown carotid artery calcification to be a statistically significant predictor of carotid artery stenosis, the odds ratio of 2.4 provides the clinical significance for radiologists to routinely report its presence and thus inform the referring dentist.

For dentists, the incidental finding of carotid calcification on an OPG should prompt a referral to the patient's general practitioner for assessment of their vascular risk factors. Importantly, this study excluded patients with previously established carotid artery disease or cerebrovascular ischaemic symptoms and thus the findings do not provide further clinical insights into these patients.

Impact on healthcare

Almost 1 million panoramic x-rays are billed through Medicare each year, and approximately 350 000 of these are in individuals 45 years of age and over.[19] Based upon our estimated prevalence of 11%, approximately 40,000 asymptomatic dental patients could have carotid calcification identified on their OPG and be referred for carotid ultrasound. This would be a huge clinical and financial impost on the already heavily burdened healthcare system. Thus, the implications of essentially mandating carotid ultrasound examination in patients with incidental carotid artery calcification, needs to be closely considered.

Firstly, the finding of a significant carotid stenosis in patients with carotid artery calcification is a surrogate endpoint and not a clinical outcome. However, the Rotterdam Study[4] has shown a strong association between carotid artery calcification and stroke. Furthermore, the Northern Manhattan Study[20] also

showed that carotid artery calcification was an independent risk factor for vascular events. Hence, carotid artery calcification has been directly associated with vascular events although its low sensitivity does not justify it as a screening tool.

Secondly, the association of clinical outcomes with carotid artery stenoses ≥50% on ultrasound needs to be placed in clinical context. The incidental detection of CAC during a routine OPG should prompt the clinician to enquire if the patient has any cerebral ischaemic symptoms. If so, then an urgent carotid ultrasound should be undertaken and referral to an appropriate specialist. However, if the patient does not have any cerebral ischaemic symptoms then follow carotid ultrasound is still required since the risk of stroke with an asymptomatic ≥50% stenosis is 5–20% per year.[21] Although contemporary stroke guidelines do not recommend routine ultrasound screening for carotid stenoses, they do recommend regular medical review of these patients to initiate medical therapy that will reduce cardiovascular events.[13,14] Accordingly, the detection of a carotid stenosis ≥50% will provoke a guideline-based change in medical therapy. Furthermore, vigilant screening for cerebrovascular symptoms in these patients with asymptomatic disease will ensure prompt revascularisation treatment if required.

Finally, the cost-benefit of performing a screening for carotid ultrasound in patients with asymptomatic carotid artery calcification needs to be considered. Yin and Carpenter[22] reported on the cost-effectiveness of routine carotid ultrasound screening in the general asymptomatic population. They concluded that the clinical benefits derived from endarterectomy outweighed the costs of the carotid ultrasound if the prevalence of a carotid stenosis within a population was more than 4.5%. Considering that the prevalence of a carotid stenosis in asymptomatic patients with carotid artery calcification is 15.4%, the decision to perform the ultrasound appears justified.

Study limitations

As alluded to above, the primary endpoint of this study is an imaging surrogate rather than a cardiovascular outcome and thus the clinical implications of the study are based on clinical guideline recommendations in asymptomatic patients with a ≥50% carotid stenosis. Furthermore, the study findings are based upon a dental population undergoing routine OPG and might not necessarily apply to other cervical radiographs. Many potential participants did not take part, and while the numbers were similar in both the CAC positive and CAC negative groups, this might have had an impact on the results. The participants were not aware if they were CAC positive or negative. Finally, more than half of all the original OPG examinations did not show the carotid region, which was not important for the dental diagnostics, but could have an impact on the prevalence of carotid artery calcification present in the population.

CONCLUSION

In a representative population undergoing OPG examination for dental diagnostic purposes, approximately 11% will have carotid artery calcification detected by an experienced dental radiologist. This finding should be routinely reported to the referring dentist since approximately 1 in 7 patients with carotid calcification is likely to have a carotid stenosis ≥50%, compared with 1 in 20 patients without carotid artery calcification on OPG. Dentists who are informed of carotid artery calcification on OPG should arrange for the patient to have further evaluation of their vascular risk factors and carotid artery ultrasound. If the patient has any cerebral ischaemic symptoms, this evaluation should be undertaken on an urgent basis. Given the findings of previous studies on the cost-effectiveness of carotid artery ultrasound in patients with carotid artery calcification, combined with the prevalence of 15%, it is likely that carotid artery ultrasound in an asymptomatic population group is also justified. Further studies are required to specifically assess the cost benefits of this strategy in reducing future cardiovascular events.

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Chapter Two

Panoramic dental x-rays and the risk of stroke

The CACO (**C**arotid **A**rtery **C**alcification on **O**PG) study is an example of how diagnostic information obtained from a radiological study can be maximised and used to assist diagnosis of conditions not specifically requested at the time of the study. A panoramic dental x-ray, commonly known as an orthopantomogram or OPG, is frequently requested by dentists and other oral health practitioners to assess the dentition, alveolar bone supporting the teeth, dental restorations and temporomandibular joints[51, 52]. Other anatomical areas are also visible on this radiograph, including parts of the cervical spine, facial bones, maxillary sinuses and soft tissues of the neck. Diagnoses of conditions such as cervical spine osteoarthritis and some forms of sinus disease can be made incidentally on these x-rays, which may be useful but are rarely of major clinical significance. Vascular calcification can also be seen, which is very common in the elderly, but does not always indicate vascular narrowing which is the sequela of atherosclerosis[53-55].

During this study, over 12 000 panoramic films were examined for the presence of carotid artery calcification. All of the orthopantomograms had been requested by dental health professionals for dental diagnostic purposes. Based on the findings on these images, age and gender matched individuals were invited to undergo a carotid artery ultrasound scan to accurately measure the degree of narrowing of the carotid arteries. The results of the ultrasound scans were recorded as showing a stenosis of less than fifty percent, or fifty percent or more. It has been previously established that a narrowing of less than fifty percent does not require either follow-up or

treatment because the risk of a cerebrovascular accident is very low, and the treatment is not justified either financially or medically due to the risks associated with vascular surgery or anticoagulation[56, 57]. Once a stenosis reaches fifty percent of the arterial diameter, follow-up to monitor the progression of atheromatous disease is recommended. As the stenosis approaches seventy percent, surgical repair is considered, as the risk of stroke now exceeds the risks of surgical complication[56, 57].

Carotid artery calcification was visible of the panoramic dental x-ray in 10.8% of the individuals in this study. When the carotid arterial diameter of the participating subgroup with carotid artery calcification on OPG were compared with participants from the group without carotid artery calcification on OPG, there was a difference between the two groups. Individuals with carotid artery calcification on their x-rays had a one in seven likelihood of having a carotid artery stenosis that required monitoring or intervention. Individuals without carotid artery calcification on their x-rays had a one in twenty likelihood of having a clinically significant carotid artery narrowing. None of the participants had any neurological symptoms or history of transient ischaemic attacks. While the difference was not statistically significant, it is clinically significant given the consequences of a cerebral event, and carotid artery calcification on OPG was a statistically better predictor than smoking which is a well-recognised risk factor for stroke[58]. That is not to say that panoramic x-rays should be used as a screening tool for carotid artery disease. The sensitivity of OPG for identifying significant carotid stenosis was 77% and specificity was 47%, confirming that it is not a good screening study, because a useful screening test needs both a high sensitivity and specificity. Given that x-rays involve ionising radiation, there is the potential, although small, for harm to occur. The mass screening of the population for

carotid artery stenosis is not recommended, even with a proven modality such as ultrasound. However, if the x-ray has been performed for other reasons, it makes good sense to utilize that image to the maximum.

A likelihood of one in seven patients with carotid artery calcification on OPG having a significant carotid stenosis, and therefore risk of stroke, could mean a substantial increase in the number of ultrasound scans being performed. There is no known health risk from a carotid artery ultrasound scan, but the financial burden could be profound. If every patient with carotid calcification was referred for a carotid ultrasound scan, as many as 40 000 individuals could be referred for a Medicare eligible scan every year. This would impose a significant cost on society. The current rebate in 2019 for a carotid artery ultrasound is $84.75[59] with many providers also charging a "gap" payment. Hence, this could potentially add an extra 3.4 million dollars to the Medicare bill each year. If one in seven of these people have a clinically significant carotid stenosis, then the extra cost of follow-up ultrasound scans, medical appointments, medication and surgical procedures is added to this number. It should also be remembered that these are asymptomatic people being considered in this study, so the validity must be considered in terms of clinical outcomes, which is stroke prevention.

The Deloitte Access Economics study into stroke in Australia 2017[60] reports that there were 56 000 strokes in Australia that year. It is not known how many of these victims were asymptomatic prior to their cerebrovascular event, although it is reported around 15% of embolic strokes are preceded by a transient ischaemic attack[61]. Ten to twenty percent of strokes are haemorrhagic rather than embolic[62].

The economic impact of stroke in this country is estimated to be $5 billion per annum. Sixty-five percent of survivors have a deficit that means they cannot live without assistance, and thirty percent of still of working age, which means they may not be able to continue to produce an income. There is little doubt that cost of these ultrasounds is minimal compared with the costs of a significant stroke, especially when one considers the neurological consequences of a stroke are permanent, and therefore costs are ongoing. These are only the financial costs that can be calculated, the psychological costs to both the stroke sufferer and their families are incalculable.

While the added ultrasound scans will produce an extra financial burden upon the health system, if only a small number of cerebrovascular accidents can be prevented, the scans become financially beneficial to the community. Although the presence of carotid artery calcification on dental panoramic x-rays was not a statistically significant predictor of carotid artery stenosis, and therefore stroke risk, the likelihood of one in seven people having a clinically significant stenosis if calcification is seen, and the permanent and often devastating effects of a cerebrovascular accident make the finding medically significant, and further investigation seems totally justified.

Chapter Three

Panoramic dental x-rays in the diagnosis of sinus disease

Statement of Authorship

Title of Paper	**Panoramic radiography is of limited value in the evaluation of maxillary sinus disease.**
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
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Principal Author

Name of Principal Author (Candidate)	Sarah Constantine
Contribution to the Paper	• Original study concept • Literature search • Reading of all panoramic images and CT scans • Statistical interpretation • Final paper preparation
Overall percentage (%)	70%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 28/4/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Dr Bruce Clark
Contribution to the Paper	• reading of all panoramic images • paper preparation
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Name of Co-Author	Dr Andreas Kiermeier
Contribution to the Paper	• study design • statistical analysis and interpretation
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Contribution to the Paper	• statistical interpretation • paper preparation
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Panoramic radiography is of limited value in the evaluation of maxillary sinus disease

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Objectives. The aim of this study was to determine (1) the diagnostic efficacy of orthopantomography (OPG) in the diagnosis of sinus diseases by using cone beam computed tomography (CBCT) as the imaging gold standard, (2) which diseases can be diagnosed by using panoramic radiography or CBCT, and (3) the interobserver agreement of 2 experienced dental radiologists.

Study Design. The images of 714 individuals who underwent OPG and CBCT on the same day were assessed separately by 2 dental radiologists. The results were compared by using Gwet's AC_1 statistical methods.

Results. In total, 1322 maxillary sinuses were imaged. The sensitivity of OPG for the detection of any maxillary sinus pathology was poor compared with CBCT, but the specificity was high. The sensitivity of OPG for detecting mucosal thickening was 36.7%. The positive predictive value of OPG for diagnosing mucosal thickening was 79.9 %, but the negative predictive value was 51.9%. Interobserver agreement was strong (≥0.912) for all lesions except mucosal thickening.

Conclusions. Panoramic imaging has low efficacy in the diagnosis of sinus disease, even when examined by experienced dental radiologists. OPG can be useful in excluding disease, but 3-dimensional scanning is necessary for the definitive investigation of sinus lesions. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:237−246)

Panoramic radiography, also known as the orthopantomography (OPG), is commonly used in the investigation of facial and dental pain. This radiographic modality shows the bones of the jaws, teeth, and supporting structures including the temporomandibular joints and the maxillary sinuses, which can all be contributors to facial pain. In this tomographic technique to obtain these images, a thin "focal trough" along the dental arch is used to produce a 2-dimensional image of the jaws. A disadvantage of the technique is that structures outside the focal trough can be blurred or not visible at all. The maxillary sinuses generally extend between 28.9 mm and 47.6 mm in the anteroposterior diameter,[1] which is deeper than the focal trough that is designed to encompass the alveolar bone. The panoramic image includes only a portion of the maxillary sinuses, which might limit the value of this radiographic technique for the diagnosis of sinus lesions.

Computed tomography (CT) and cone beam computed tomography (CBCT) are often considered the radiographic gold standard for imaging the sinuses.[2,3] Although the images are anatomically accurate, CT and CBCT have a number of disadvantages compared with OPG, including a higher radiation dose to the patient and a much higher financial cost that is not always covered by insurance. CBCT is widely available for use in dental medicine, but usually, there is limited access to CT, and this restricts referrals from general dental practitioners. For these reasons, panoramic imaging continues to be used as the first line of investigation of the maxillary sinuses in the majority of patients.

There is paucity of published studies investigating the beneficial effects of OPG in the diagnosis of maxillary sinus disease. Most studies have been performed on a small number of patients, and the radiographs have not always been interpreted by a specialist in dental or oral and maxillofacial radiology. Only 4 studies have compared panoramic imaging and CT or CBCT

Statement of Clinical Relevance

Panoramic dental imaging is of limited value in the investigation of maxillary sinus disease. The increased cost and radiation dose of cone beam computed tomography is outweighed by the diagnostic accuracy of the technique in the diagnosis of sinus disease.

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with respect to sinus disease.[4–7] All these studies found CT or CBCT to be more accurate than panoramic imaging in the diagnosis of sinus disease, but there was marked variability in the sensitivity and specificity found for panoramic imaging, and none of these studies included more than 100 patients. Several articles have compared the 2 imaging modalities with specific reference to third molar root relationships and sinus septations, with similar results.[7–10]

The primary objective of this study was to determine the sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) of panoramic imaging in the diagnosis of different sinus diseases with use of CBCT as the imaging gold standard. The secondary aim was to determine which sinus diseases can be detected on panoramic images and which lesions require cross-sectional imaging to make the diagnosis. The final objective was to examine the interobserver reliability between 2 experienced dental radiologists in the diagnosis of sinus pathology with the use of OPG.

MATERIALS AND METHODS

The study was approved by the University of Adelaide Human Research Ethics Committee, which waived the need to obtain informed consent. This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

OPG and CBCT were performed on 714 adult patients (age 18 years or greater) for dental diagnostic purposes (Table I). Indications for imaging included orthodontic evaluation, investigation of oral pain, and implant planning. Both imaging techniques were performed on each patient on the same day, and thus both imaging techniques are representative of the same anatomy and pathology. All referrals were received from fully qualified specialist oral surgeons, orthodontists, periodontists, and endodontists. Both imaging techniques were performed at the request of the referring dentist, with the CBCT scan frequently limited to the maxilla or only a part of the maxilla.

All images were taken by using a Vatech Reve3-D combined panoramic/CBCT unit (Vatech, Gyeonggi, ROK) by qualified radiographers. Image parameters were selected on the basis of patient size and clinical information provided on the referral.

Table I. Demographic data of patients included in the study

		Age		
Gender	*N (%)*	*Min*	*Mean*	*Max*
Male	312 (43.7%)	18.8	51.7	89.7
Female	402 (56.3%)	18.9	54.0	90.3

Data collection

A sample size calculation was undertaken on the basis of the findings of Tadinada,[4] Martinez-Gonzalez,[5] and Nah,[6] and the sensitivity of dental OPG for detecting sinus disease was found to be 22% to 66%. Sample size calculations were performed by assuming a prevalence of 30% (based on mucosal thickening), sensitivity of 50%, and a desired margin of error of 10% for a 95% confidence interval, which indicated that a minimum of 321 patients was required.[11]

Every OPG image was evaluated independently by 2 specialist dental/head and neck radiologists. The first (S.C.) had 10 years of specialist experience in dental radiology, and the other (B.C.) had 40 years of specialist experience in dental radiology. Both radiologists were experienced in the interpretation of panoramic images, as well as craniomaxillofacial CT and CBCT images. Each maxillary sinus was examined for the presence of mucosal thickening, mucosal polyps/mucous retention cysts, fluid in the sinus, odontogenic sinusitis, mucoceles, oroantral fistulas, or tumors. Each disease was recorded as "present" if the radiologist could confidently diagnose on the basis of the OPG image, or "absent" if a diagnosis could not confidently be recorded on the basis of the OPG alone. The CBCT scans were read by only one of the radiologists and served as the gold standard.

The following definitions were used:

- *Mucosal thickening:* The normal maxillary sinus mucosa is between 0.2 and 0.8 mm in thickness.[12] Mucosa of greater than 1-mm thickness was recorded as "mucosal thickening" in the maxillary sinus. The mucosal thickening had to involve the majority of the floor of the sinus to be recorded as thickened on CBCT scans (Figure 1).
- *Mucosal polyp/mucous retention cyst:* The densities of these lesions were very similar, and it was not possible to accurately differentiate between them on imaging. A polyp/cyst was considered to be present if there was focal thickening of the sinus mucosa of greater than 5 mm (Figure 2).
- *Sinus fluid:* Fluid was deemed to be present if a horizontal shadow with a meniscal edge was present (Figure 3).
- *Odontogenic sinusitis:* The presence of mucosal thickening or polyps/cysts that are in direct contact with periapical lesions were determinants of odontogenic sinusitis (Figure 4).
- *Mucocele:* A mucocele was considered present if the sinus was opacified and expanded, with thinning of the bony walls (Figure 5).
- *Oroantral fistula:* The diagnosis of an oroantral fistula was made if a bony dehiscence was detected in

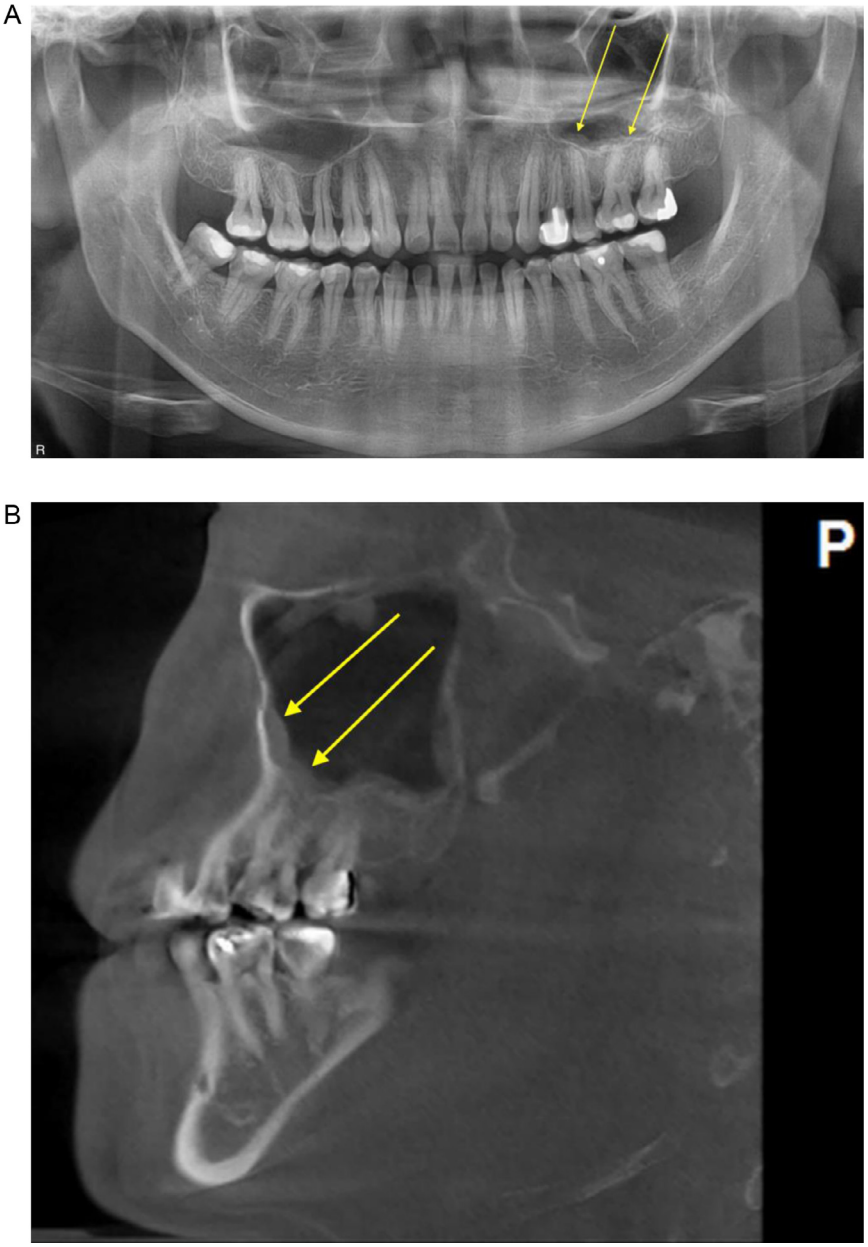

Fig. 1. **A**, Orthopantomography (OPG) image showing mucosal thickening in the left maxillary sinus *(arrows)*. **B**, Sagittal cone beam computed tomography (CBCT) image in the same individual showing mucosal thickening in the left maxillary sinus *(arrows)*.

the floor of the maxillary sinus and if it communicated with the oral cavity (Figure 6).

- *Tumor:* The presence of bone destruction is the hallmark of malignant sinus tumors. No tumors were found in this study.

The CBCT scans that were evaluated by the specialist dental radiologist (S.C.) were read by using Osirix DICOM (Digital Imaging and Communications in Medicine) viewer software enabling multiplanar reconstructions in the sagittal, coronal, axial, and oblique planes. Each sinus was evaluated by using the same criteria listed above. The OPG images were not available when the CBCT scans were evaluated, and the scans were read several weeks after the panoramic images to ensure that there was minimal crossover bias.

All data manipulations were undertaken in the open-source statistical software R v3.4.3.[13] For each sinus disease, the estimation of sensitivity and specificity of OPG (with CBCT as the gold standard) took into account the relationship between the left and right sides of each patient, using the variance inflation factor

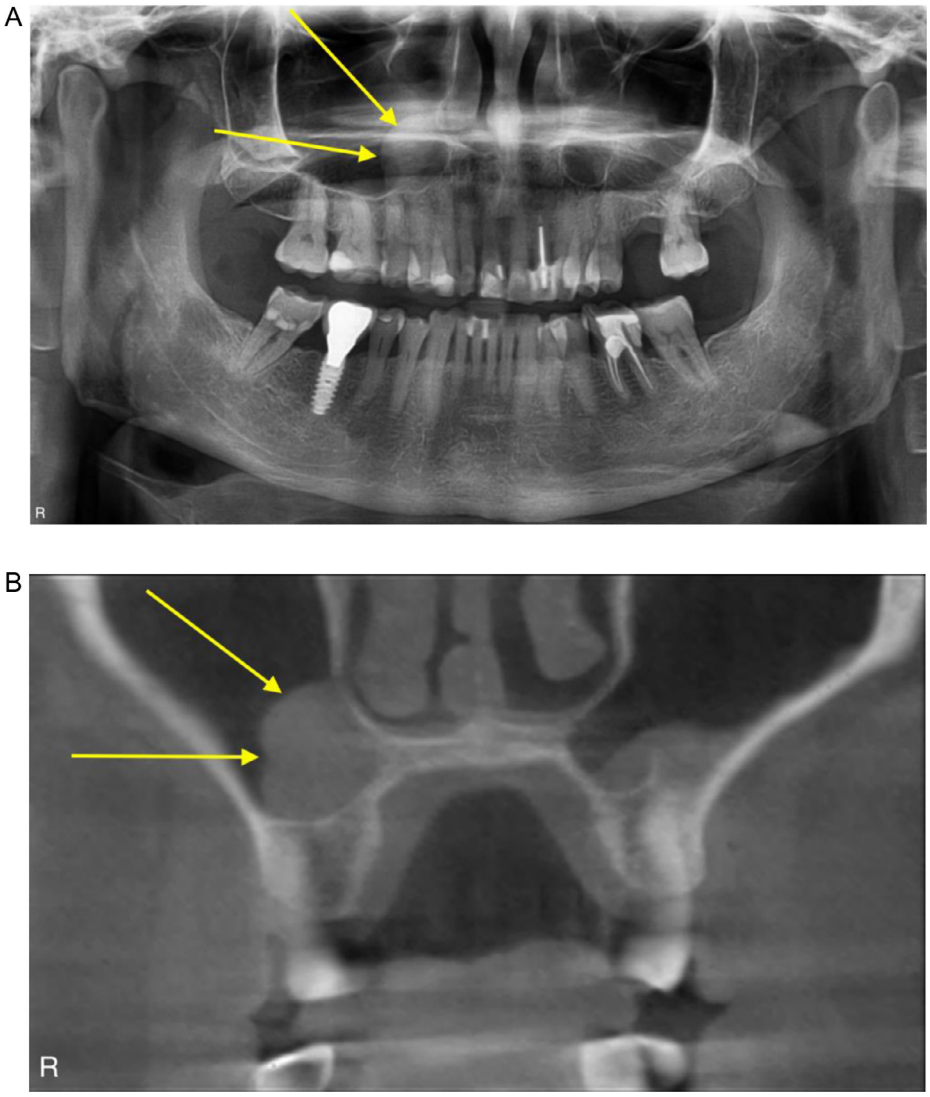

Fig. 2. **A**, Orthopantomography (OPG) image showing a polyp or mucous retention cyst in the right maxillary sinus *(arrows)*. **B**, Cone beam computed tomography (CBCT) image in the same individual showing a polyp or mucous retention cyst in the right maxillary sinus *(arrows)*.

approach described by Genders et al.[14] This was done because even though CBCT was considered the gold standard, it is unlikely to be 100% accurate. [15] The interobserver agreement was estimated for each sinus disease by using Gwet's AC_1, which is preferable to Cohen's Kappa.[16] The interpretation of AC_1 is similar to Kappa—that is, AC_1 varies between 0 and 1, where 0 denotes complete disagreement, and 1 denotes complete agreement, and intermediate values can be assessed by using the same scales that are used for Cohen's Kappa ($\leq$0.2 = poor; 0.21−0.40 = fair; 0.41−0.60 = moderate; 0.61−0.80 = good; 0.81−1.0 = very good).[17] This was done separately for each side because there is no readily available measure that can take clustering into account; the AC_1 estimates for the 2 sides were found to be very similar, and hence their averages were reported.

RESULTS

Participant demographic characteristics

A summary of the demographic characteristics of the participants is given in Table I.

Sensitivity, specificity, and predictive values

Data were collected from 714 patients. Of these, 19 were excluded from the comparison of OPG with CBCT because neither of the maxillary sinuses had been fully imaged on CBCT. A total of 1322 maxillary sinuses were imaged (658 right sinuses, 664 left sinuses) because 68 patients had CBCT of only one side of the maxilla (37 right side only, 31 left side only).

The prevalence of maxillary sinus pathology detected on CBCT is shown in Table II.

More than half the sinuses showed mucosal disease, and disease was bilateral in 263 patients. The

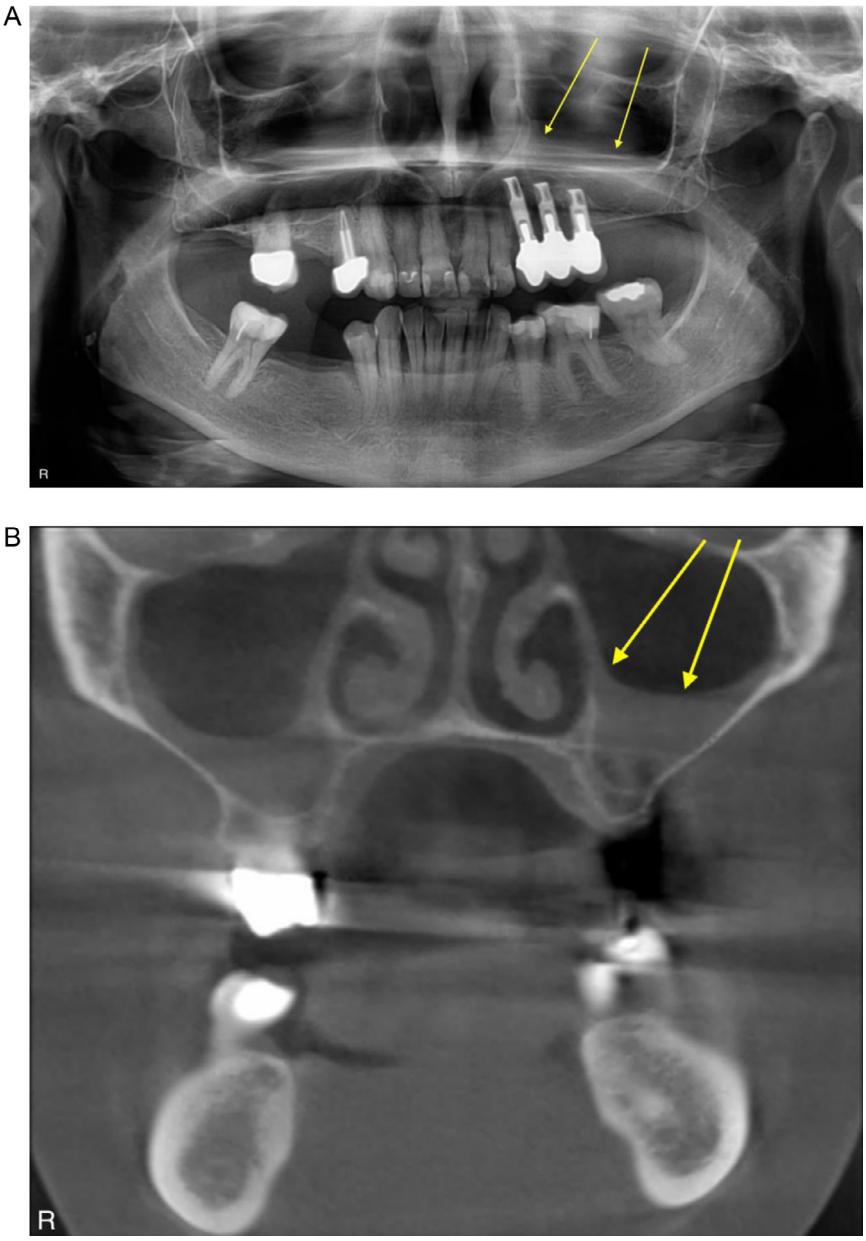

Fig. 3. **A**, Orthopantomography (OPG) image showing the meniscal edge associated with fluid in the maxillary sinus *(arrows)*. **B**, Coronal cone beam computed tomography (CBCT) image in the same individual showing the meniscal edge associated with fluid in the maxillary sinus *(arrows)*.

presence of 2 of more lesions was also common, and all involved mucosal thickening. Two diseases were observed in 208 sinuses (15.7%), and 3 lesions were observed in 22 sinuses (1.7%).

Data on the sensitivity, specificity, PPV, and NPV of panoramic imaging in the detection of sinus disease compared with CBCT are provided in Table III.

In all of our observed findings, the sensitivity of OPG for the detection of any maxillary sinus pathology was poor compared with CBCT scanning (≤36.7%), and specificity was high (≥88.1%). The PPV of OPG for correctly diagnosing mucosal thickening was 79.9%, but the NPV was only 51.9%.

Interobserver agreement

Panoramic images were reviewed for a total of 714 patients by both radiologists. The average AC_1 values (based on separate calculations for left and right sides) are given in Table IV.

There was very high agreement (≥0.912) in all reported diseases except the presence of mucosal

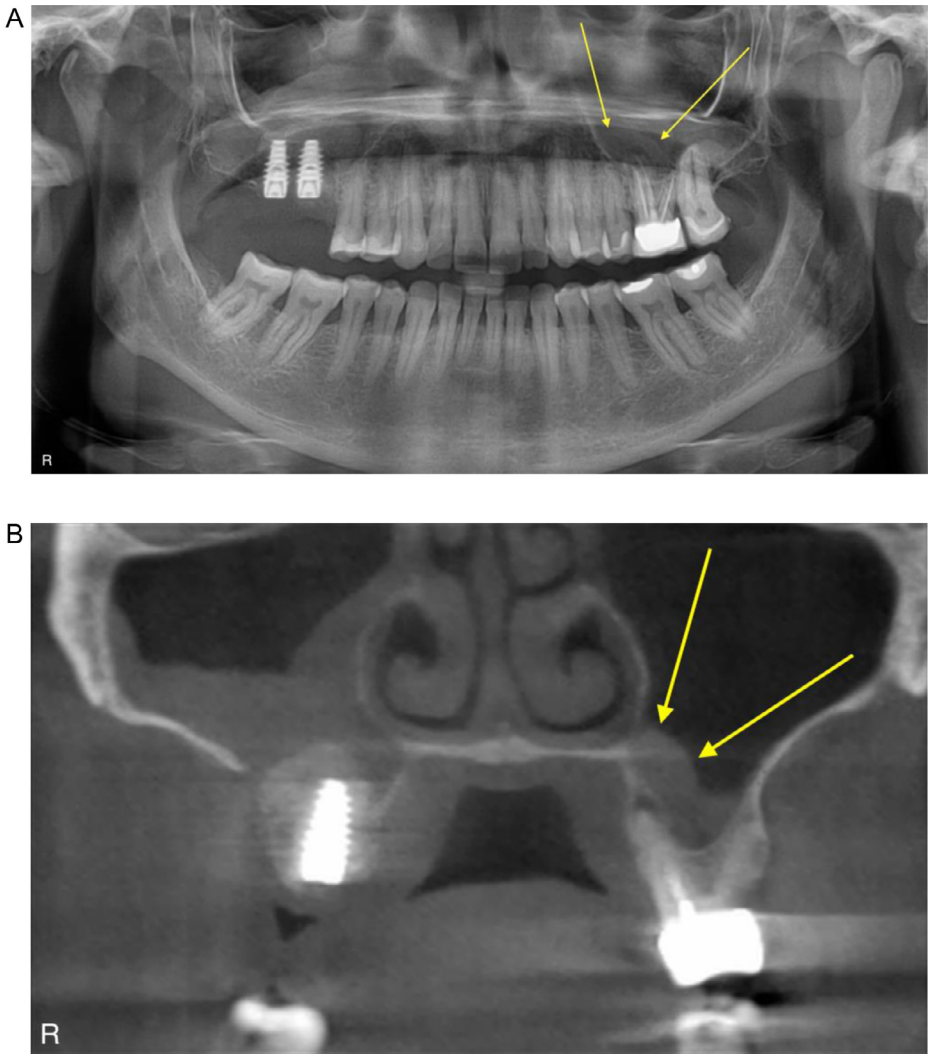

Fig. 4. **A**, Orthopantomography (OPG) image showing a periapical lesion on the left maxillary first molar with associated sinus disease representing odontogenic sinusitis *(arrows)*. **B**, Coronal cone beam computed tomography (CBCT) image in the same individual showing a periapical lesion on the left maxillary first molar with associated sinus disease representing odontogenic sinusitis *(arrows)*.

thickening (0.677). One radiologist (S.C.) reported mucosal thickening more often than did the other (B.C.).

DISCUSSION

CT and CBCT have been the "gold standard" for imaging the paranasal sinuses for many years. Despite this, the higher cost and higher radiation dose, compared with plain radiography, have resulted in OPG continuing to be used for diagnosis when surgery is not immediately being considered. We found the sensitivity of diagnoses based on OPG for detecting mucosal thickening was only 36.7%, and the NPV of 51.9% was little better than flipping a coin to exclude disease. The sensitivity in detecting other sinus pathoses was even lower, although the high NPV in these conditions lends to the utility of panoramic imaging in excluding these abnormalities.

Hayfever and allergic rhinitis affect around 20% of Australians, with 8.4% reporting chronic sinusitis.[18] The incidence in South Australia is slightly higher than the national average, with 21.3% of residents reporting symptoms of hayfever/allergic rhinitis,[18] a rate that is slowly increasing. Most findings of mucosal thickening in the absence of an upper respiratory tract infection can be attributed to the increasing rate of allergies in our population. The prevalence of 56.3% for mucosal thickening in our study is more than double the reported population average. This can be attributed to the percentage of individuals with odontogenic sinusitis (11.6%) who were also included in the mucosal thickening group and to the likelihood that many of the

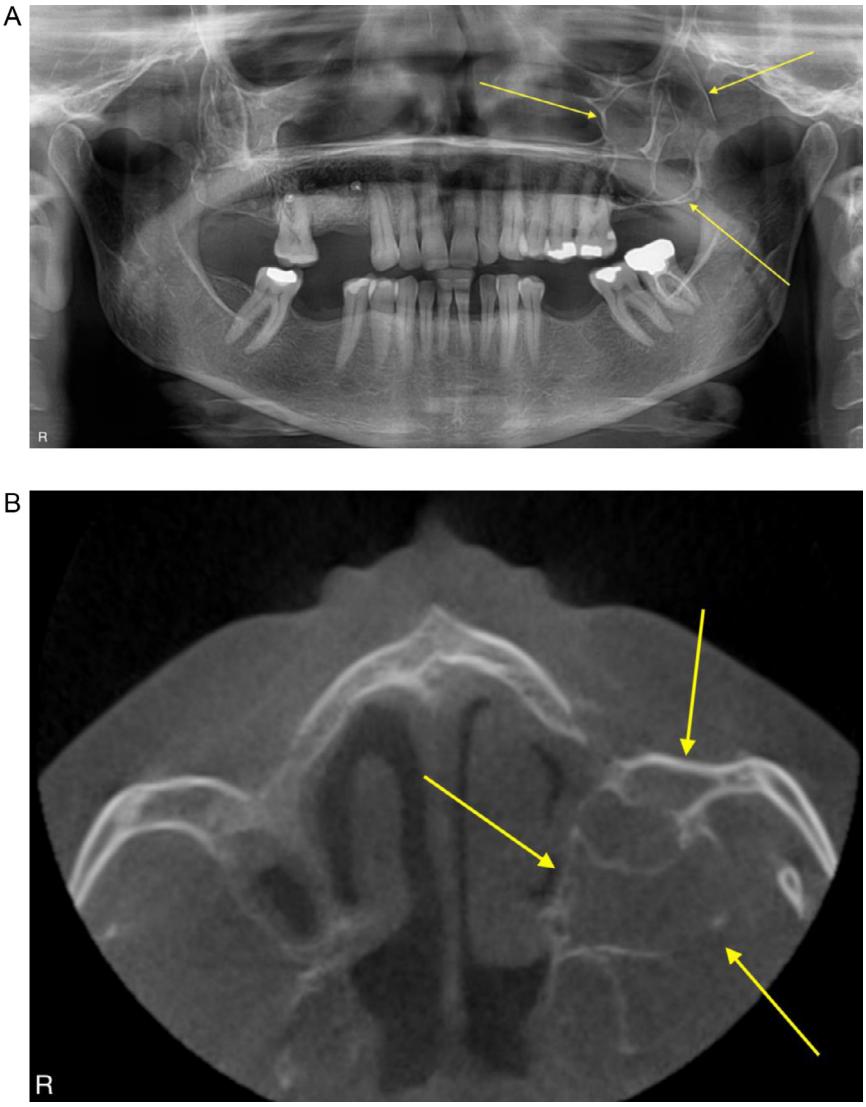

Fig. 5. **A**, Orthopantomography (OPG) image showing the opacified and expanded left maxillary antrum caused by a mucocele *(arrows)*. **B**, Axial cone beam computed tomography (CBCT) image in the same individual showing the opacified and expanded left maxillary antrum caused by a mucocele *(arrows)*.

population with mild mucosal thickening or mucus retention cysts are asymptomatic and would, therefore, not report the presence of these conditions in the National Health Survey. It is well known that the correlation between sinus disease and sinus symptoms is poor.[19–21]

Tadinada et al.[4] found a high prevalence of sinus disease in their small cohort of patients, although they did not differentiate among the various diseases. When comparing OPG to CBCT, they also found an NPV that was little better than chance. Martinez-Gonzalez et al.[5] reported similar results in their slightly larger cohort of patients, with OPG-detected sinus pathology in less than a third of patients with disease detected on CBCT. These findings correlate well with our results. Nah et al.[6] had more success with panoramic imaging, with approximately two-thirds of OPG findings correlating with findings on CBCT, a rate that is higher than most other studies. Shahbazian et al.[7] found that diagnostic results from panoramic imaging were very poor for odontogenic sinus disease compared with CBCT (7.6%). This finding is quite different from that in our study, which showed a much higher correlation. However, our patient numbers were substantially larger (714 vs 157).

The present study found that OPG was more useful in the investigation of odontogenic sinusitis than that of most other sinus conditions. The PPV of 80.6% and NPV of 90.7% indicate that the dental professional can be reasonably sure of the presence (or absence) of sinus disease caused by dental pathology without proceeding to CT or CBCT scanning. The incidence of

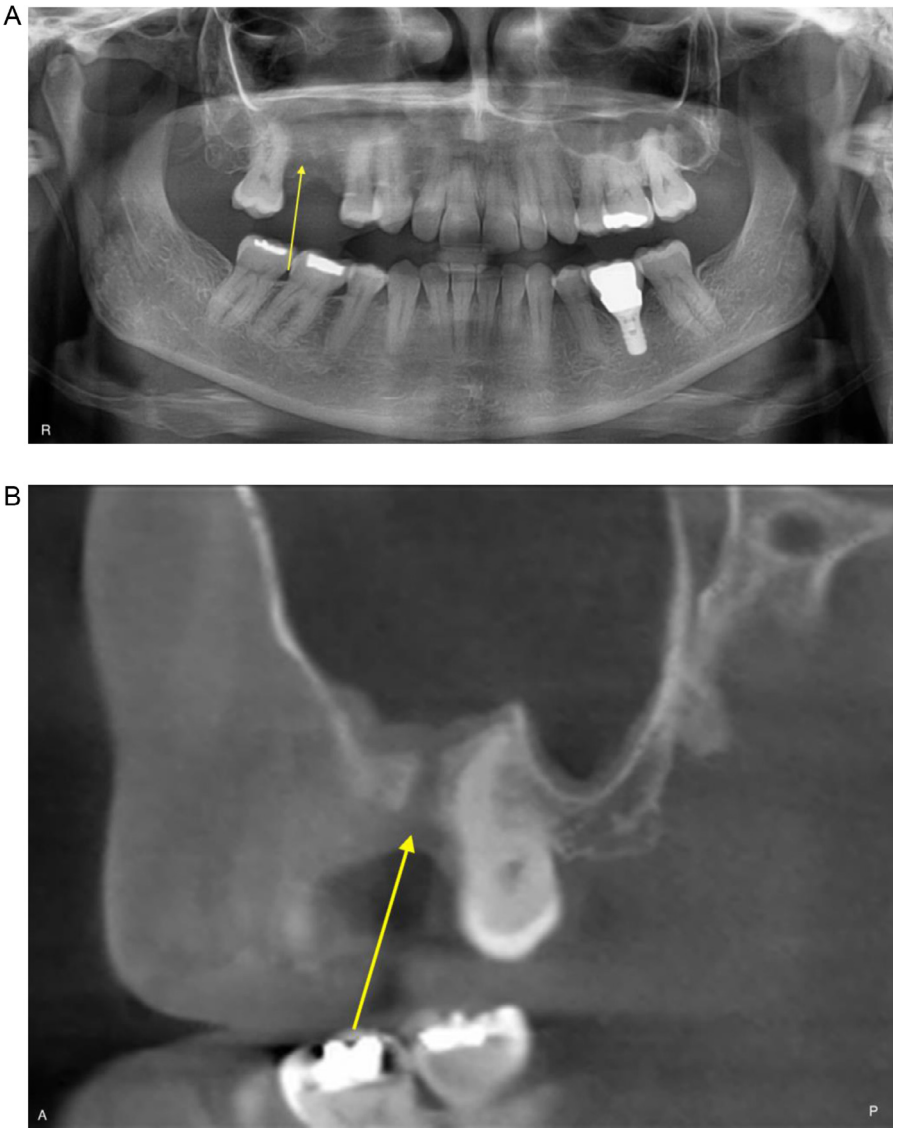

Fig. 6. **A**, Orthopantomography (OPG) image showing a small bony dehiscence in the floor of the maxillary sinus, indicating an oroantral fistula *(arrows)*. **B**, Cone beam computed tomography (CBCT) image in the same individual showing a small bony dehiscence in the floor of the maxillary sinus, indicating an oroantral fistula *(arrows)*.

Table II. Sinus pathology detected on cone beam computed tomography scanning

	Number of affected sinuses	*Percentage (%)*
Mucosal thickening	744	56.3
Mucosal polyp/mucus retention cyst	155	11.7
Sinus fluid	15	1.1
Odontogenic sinusitis	153	11.6
Mucocele	2	0.2
Oroantral fistula	4	0.3

odontogenic sinusitis is reported as being between 10% and 40%,[22,23] although on imaging alone it can be difficult to determine the cause of sinus disease, and clinical assessment is essential. We found a prevalence of 11.6%, based on the features of periapical disease in direct contact with mucosal thickening in the maxillary sinus. This figure may change when also taking into account the clinical features. Odontogenic sinusitis is generally thought to be under-recognized,[22–25] and the prevalence may be higher than our figure.

Table III. Estimates of sensitivity and specificity (including 95% confidence interval [CI]), by using adjusting for clustered patient data (i.e., sides)

	Sensitivity (%)	*95% CI*	*Specificity (%)*	*95% CI*	*Positive predictive value (%)**	*Negative predictive value (%)**
Mucosal thickening	36.7	32.6–40.8	88.1	85.1–91.0	79.9	51.9
Polyp/mucus retention cyst	31.6	23.6–39.6	92.5	90.8–94.3	35.8	91.1
Sinus fluid	6.7	0.0–19.4	99.9	99.8–100.0	42.7	99.0
Odontogenic sinusitis	22.2	14.9–29.5	99.3	98.8–99.8	80.6	90.7
Mucocele	0	†	100	†	‡	99.8
Oro-antral fistula	25.0		99.9	99.8 – 100.0	42.9	99.8

Blank cells indicate that the corresponding value(s) could not be estimated from the data.
*Estimates for positive and negative predictive values were calculated by using the prevalence estimates for each corresponding sinus disease (see Table II).
†Could not be estimated because the intraclass correlation coefficient was zero.
‡Could not be estimated because there was no detection using orthopantomography (OPG).

Table IV. Comparison of orthopantomography (OPG) interpretation by 2 dental radiologists

	Agreement (AC_1)[10]
Mucosal thickening	0.677
Polyp/mucus retention cyst	0.912
Sinus fluid	0.999
Odontogenic sinusitis	0.971
Mucocele	1.000
Oroantral fistula	0.999

The 2 radiologists showed good agreement in the diagnosis of most sinus conditions on the basis of panoramic imaging. There was very high agreement ($\geq$0.912) in all reported diseases except the presence of mucosal thickening (0.677). The high agreement could be attributed, in part, to the large sample size and low prevalence of these conditions. One radiologist (S. C.) reported mucosal thickening more often than did the other (B.C.).

The recognition of mucosal thickening on OPG was the one area where there was marked disagreement. We believe this reflects the difficulty in diagnosing sinus disease by using panoramic imaging. There are multiple overlying shadows involving the maxilla, including the hard and soft palates, the tongue, and often the palatoglossal air space if the tongue is not placed on the hard palate during exposure. As previously mentioned, the sinus is longer in the anteroposterior plane than in the focal trough of the image, and this can exacerbate the confusion in diagnosis. Patient rotation can also produce asymmetry in sinus density, which, in turn, can produce artefacts over the sinuses. Finally, the decision to report disease as "mucosal thickening" or "mucus retention cyst/polyp" is not always clear.

CONCLUSIONS

This study confirmed that panoramic imaging has poor efficacy in the diagnosis of sinus disease, even in the hands of experienced dental radiologists. Our study showed that OPG can be useful in excluding sinus disease, with high specificity and NPV for sinus abnormalities other than mucosal thickening. There is high interobserver agreement between experienced dental radiologists in the interpretation of sinus disease on panoramic imaging. CT and CBCT remain the gold standard for the diagnosis of sinus disease, and despite the increased cost and radiation dose, 3-dimensional imaging is necessary for the definitive diagnosis of sinus pathology.

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Chapter Three

Panoramic dental x-rays in the diagnosis of sinus disease

Just under 1 million panoramic dental x-rays or orthopantomograms are performed and billed through Medicare each year[63] in Australia, and the additional number performed that are not billed through Medicare is unknown but potentially substantial. Many dental health professionals own their own imaging equipment to allow quick and convenient x-ray image production, but are often not covered under the Medicare scheme.

Referrals under Medicare are reported by a medical or dental radiologist, and the clinical details on the referral frequently involve facial pain, swelling or concerns of maxillary sinus disease. This is not surprising, given the close proximity of the maxillary sinuses to the roots of the teeth, the maxillary permanent molars in particular. Periapical disease and dental caries may cause facial pain in the region of the sinuses and it is estimated that up to 10% of maxillary sinus disease is odontogenic in origin[64, 65]. Combine that with the high incidence of hayfever and allergic sinus disease in southern Australia[66], along with viral nasal congestion and bacterial sinus infection, and at any time a substantial proportion of the population are suffering facial pain or sinus symptoms. Many sufferers will attend their family doctor for treatment, but a large number will attend their dentist with dental pain due to the involvement of the tooth roots in sinus disease. Hence, x-ray referrals are generated from both medical and dental professionals for the evaluation of maxillary sinus disease. General dentists are restricted in the imaging they can request by both Medicare and the state radiation protection legislation across Australia, whereas all

medical professionals can refer for CT scanning. The result is that far more doctors will refer a patient directly for cross-sectional imaging rather than tomographic imaging, but dentists are restricted to panoramic films. As the dental professional is also interested in the teeth and associated structures, it seems to be reasonable that they utilize OPGs for their purposes.

Orthopantomograms use a panoramic technique to obtain images. The patient's head remains still for several seconds while the x-ray tube moves around the patient's face during the exposure to produce a two dimensional image of the three dimensional jaws. A thin focal trough is selected for the exposure which is designed to follow the dental arches and produce an image that has the dentition sharply in focus. The result is the maxillary sinuses are incompletely seen on dental panoramic imaging, which can have an effect on the diagnosis of sinus disease using this technique.

There are few published articles quantifying the effectiveness of orthopantomography in the diagnosis of maxillary sinus disease[67-70]. Serious sinus disease such as malignancy or invasive fungal disease is rare and typically symptomatic, so is appropriately referred for evaluation with CT or MRI scanning. While a technique such as orthopantomography is unlikely to be used in these serious conditions, if the images are not able to effectively diagnose maxillary sinus disease, the patient may be exposed to unnecessary radiation from a technique that does not give the required diagnostic information. This also invokes a cost on Medicare, the patient or both. The typical dose from a panoramic x-ray is 15 microSieverts (μSv) compared to a cone beam CT dose of 75 μSv and a multislice CT dose of 200 μSv[71]. Both the cone beam CT and conventional CT doses are significantly higher than

panoramic imaging, but this becomes irrelevant if the panoramic technique cannot provide the information required to make a diagnosis.

There are three main principles of radiation protection with respect to human health. The first principle is justification, which refers to the clinical reason for performing the imaging. Any exposure to medical ionising radiation needs to be justified with regards to the diagnosis and treatment of the patient. For example, it would be justified to perform imaging of a patient to evaluate the paranasal sinuses when the result of the imaging will determine whether surgery will be performed, or whether medical treatment would be used. The very small detrimental risk of the radiation dose is outweighed by the potential benefit to the patient by choosing the best possible treatment of their condition, and minimising any treatment risks. However, if the imaging will not influence or alter the management of the patient's condition, the imaging is no longer medically justified and should not be performed. This aims to minimise any unnecessary radiation exposure to patients by ensuring there is a clinical need for the imaging.

The second principle of radiation protection is optimisation. This refers to the performance of the imaging technique, both with reference to the radiation dose given to the patient, and the diagnostic quality of the images obtained. The "optimal" imaging technique involves the production of the best quality images using the lowest possible radiation dose. This encompasses the use of radiation grids and screens to reduce radiation noise and scatter, altering the radiation dose depending on patient size and the area being imaged, and appropriate patient positioning to achieve the images necessary to make a diagnosis. If an imaging procedure is medically justified,

then the images must be of the best diagnostic quality or the radiation dose to the patient does not outweigh the benefit. Hence there are many occasions where a higher radiation dose must be used, or extra images obtained to ensure a diagnosis can be made.

The third principle of radiation protection is the ALARA principle (As Low As Reasonably Achievable). Every radiological investigation must be performed at the lowest practicable dose to obtain quality diagnostic information. It is the "reasonably achievable" that is particularly important with this principle, as the radiation dose will vary substantially depending upon the equipment used, the type of examination, the anatomical area being imaged and the size of the patient. For example, in a slim patient, the lowest dose that is reasonably achievable will be significantly lower than in an obese patient to obtain a similar diagnostic image quality, and the dose for a chest x-ray will be lower than a lumbar spine x-ray in any patient as a result of the differing tissue densities.

When performing both panoramic dental x-rays and sinus CT scans, there is only a minor difference in tissue density between adult patients, and minimal variation in radiation dose when modern equipment is used. The second and third principles of radiation protection should be routinely achieved, but the first principle is the variable factor.

Our study has shown that panoramic dental films are not reliable in the diagnosis of maxillary sinus disease, even when read by radiologists with significant dental experience. This certainly raises the question as to whether there is any justification in performing an orthopantomogram for the evaluation of the maxillary sinuses. It

might seem as if there is no justification at all, however the study showed a high specificity for the exclusion of sinus pathology, including both odontogenic sinusitis and oro-antral fistulae. This is important in treatment planning, as in both these conditions, the primary treatment of the sinus disease involves treating the underlying dental cause. Given the prevalence of odontogenic maxillary sinus disease is around 10%[64, 65], this provides clinical justification for the dental professional to perform an OPG to investigate the possibility of dental related sinus disease. The justification is less clear for medical professionals. The poor sensitivity of panoramic imaging in the diagnosis of maxillary sinus disease means a negative result is not reassuring, and the imaging of the dentition is usually not of any interest to the doctor. There is also no doubt that cross-sectional imaging is essential if sinus surgery is to be performed. With modern dose reduction techniques used with CT scanning, there is little justification in performing anything other than CT scanning for the medical investigation of sinus disease.

The financial costs, while less important than patient safety, also need to be understood. The Medicare rebate for a CT scan of the sinuses is approximately five times that for an orthopantomogram[72, 73]. This could result in a significant financial burden upon the health system, however, an unknown number of patients who have an OPG may then have a CT scan of the sinuses for surgical planning anyway. While there may be a cost increase through the utilization of CT scanning as the first line investigation of maxillary sinus disease, it may be minimal if less patients have a panoramic film as well. While the radiation dose of a multislice CT scan is approximately 13 times higher than a panoramic film[71], there is still a radiation benefit if the panoramic film is not performed.

There is very little literature comparing cone beam CT with multislice CT in the diagnosis of sinus disease, and more importantly, in the effectiveness of surgical planning. The radiation dose of a multislice CT of the facial region is approximately three times the dose of a cone beam CT of the same area[71] and twice the financial cost[72, 74]. As discussed earlier, this becomes irrelevant if the imaging techniques are not of equivalent diagnostic quality. Al Abduwani et al[75] found that cone beam CT was comparable to conventional CT for the purposes of basic sinus surgery, but not for more complicated diagnoses such as sinonasal tumours where soft tissue contrast is required. De Cock et al[76] compared the image quality of both CT techniques in patients with and without sinonasal polyposis and found the image quality similar, but multislice CT was slightly better in those with disease compared to those without. Fakhran et al[77] simulated cone beam CT sequences from multislice CT scans and compared the image quality between the two scan sets. The principle aim of this study was to evaluate the presence of any clinically important findings that might be missed on cone beam CT compared to multislice CT. They found that soft tissue pathology was rare and therefore rarely missed on cone beam CT, and that cone beam CT could provide substantial radiation dose reduction benefits over multislice CT. These studies are largely comparing image quality only. The Al Abduwani et al study[75] is the only publication that makes any significant mention of the surgical appropriateness of the two data sets. There is no doubt that image quality is important, but ultimately it is the confidence of the surgeon in relying on the images that is the most important end-point. The perceived image quality must be interpreted in the surgical setting. More research is required in this area before cone beam CT can be recommended as a suitable imaging method in the surgical patient.

Although the majority of sinus surgery is for benign mucosal disease and polyposis, the proximity of the paranasal sinuses to the cranial cavity and particularly the relationship of the ethmoid air cells and sphenoid sinuses to the internal carotid arteries and optic nerves, pre-operative delineation of the sinus anatomy is critically important to avoid catastrophic complications.

Based on the findings of this study, it seems appropriate that dental practitioners continue to utilise panoramic films for the evaluation of sinus pathology in relation to the dentition, however medical practitioners should utilise CT or cone beam CT in patients where surgery is not being immediately considered, and multislice CT for surgical planning.

Chapter Four

The antenatal diagnosis of craniosynostosis

Statement of Authorship

Title of Paper	The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better.
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Publication Details	Constantine S, David D, Anderson P. The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better. Australasian Journal of Ultrasound in Medicine. 2016;19(3):91-8. DOI: 10.1002/ajum.12016.

Principal Author

Name of Principal Author (Candidate)	Sarah Constantine
Contribution to the Paper	• literature search • collection of ultrasound images • statistical analysis • main author of the final paper
Overall percentage (%)	80%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 2/3/19

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Professor David David*
Contribution to the Paper	• original concept of the study • literature search/background information • supply of ultrasound scans • final paper preparation *** Prof David has now retired, and despite efforts we were unable to contact him. Prof Anderson has signed on his behalf.**
Signature	Date: 28/6/2019

Name of Co-Author	Professor Peter Anderson
Contribution to the Paper	• literature search/background information • collection of patient details • final paper preparation
Signature	Date: 28/6/2019

Statement of Authorship

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iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better

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Abstract

Introduction: The cranial sutures allow for growth of the developing brain in both the pre- and post-natal period but also play a crucial role in vaginal delivery. Birth problems are commonly reported by the mothers of children with craniosynostosis and, in particular, sagittal synostosis.

Methods: Patients presenting with all forms of craniosynostosis were identified through a search of computer records, and the antenatal imaging was obtained and examined. The fetal cranial measurements including biparietal diameter, occipitofrontal diameter and head circumference were recorded, and the cephalic index (CI) was calculated for each affected fetus. A birth history was also recorded.

Results: Scans in both the second and third trimesters were available for 28 fetuses who had sagittal synostosis. Eight fetuses (29%) had a significant reduction in CI (>3) between the morphology and growth scans. There was an increase in the number of emergency caesarean deliveries in women whose fetuses had sagittal synostosis when compared with the general population (22% vs. 17%).

Conclusion: The calculation of CI can be performed routinely at antenatal scanning. A value outside the normal range or a change in CI during the pregnancy should prompt detailed scanning of the fetal skull and cranial sutures. This will assist obstetricians with delivery planning.

Keywords: craniosynostoses, fetal ultrasound, prenatal, scaphocephaly, ultrasonography.

Introduction

Craniosynostosis occurs in approximately 1 in 2500 live births.[1] Most of these are isolated (non-syndromic) sutural fusions with 15% occurring as part of a craniofacial syndrome.[2] The antenatal diagnosis of severe conditions such as Pfeiffer, Crouzon and Apert syndromes is often made antenatally via morphology ultrasound scanning, whereas non-syndromic sutural stenoses are uncommonly detected with ultrasound.[3] Many do not see this as a significant issue as there is no antenatal treatment available for craniosynostosis. When the more severe syndromes are diagnosed antenatally, many parents elect to terminate the pregnancy.

The cranial sutures allow for growth of the developing brain in both the pre- and post-natal period but also play a crucial role in vaginal delivery. The patent sutures allow moulding of the fetal skull to facilitate passage through the birth canal. There are only a handful of published reports that describe the delivery problems associated with craniosynostosis, in particular sagittal synostosis,[3–5] and the morbidity to both mother and child as a result.

This article discusses the effects of craniosynostosis on vaginal delivery and the need for increased awareness of the condition at antenatal scanning, with particular emphasis on sagittal synostosis.

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Methods

This retrospective study was approved by the Women's and Children's Health Network Human Research Ethics Committee, which waived consent.

The Australian Craniofacial Unit is Australia's leading surgical unit for the diagnosis and management of craniofacial disorders. It is based in Adelaide, South Australia (SA), and manages patients from all over Australia and South-East Asia. The majority of the pre- and post-surgical imaging for both paediatric and adult patients is performed at the Women's and Children's Hospital (WCH) in Adelaide.

Patients presenting to the WCH with all forms of craniosynostosis were identified through a search of computer records. The antenatal imaging for patients born between 1 January 2000 and 31 December 2014 was traced, and the ultrasound reports and images were obtained where possible. Imaging for some older patients was no longer available, and antenatal scans performed outside SA and Northern Territory (NT) were not traced. These patients were excluded from the audit. Pregnancies that did not result in the birth of a live child were also excluded from analysis.

The fetal cranial measurements including biparietal diameter (BPD), occipitofrontal diameter (OFD) and head circumference (HC) were recorded. These measurements were either recorded at the ultrasound scan or were measured on the computer images. Measurements were recorded from the morphology scan (performed between 17 and 23 weeks) and a third trimester growth scan. If several growth scans were performed in pregnancy, the scan performed closest to 32 weeks' gestation was selected. The gestation at delivery and the type of craniosynostosis were also noted.

The cephalic index (CI) was calculated for each affected fetus from measurements obtained at each scan using the formula (Jeanty *et al.*[6]):

$$CI = BPD/OFD \times 100$$

Any change in CI was noted between the morphology and growth scans. The CI was considered normal if between 75 and 85.[6,7] The available images were also reviewed for any visible signs of craniosynostosis.

The method of delivery of each child was recorded, including the reason for any interventional deliveries. Where the information was available, pelvic injuries to the mother as a result of the delivery were also recorded. Data were compared to the state-wide data provided by the South Australian Pregnancy Outcome Unit (unpublished data).

Results

There were 229 children born in SA/NT during the 15-year audit period who have been diagnosed with craniosynostosis.

One hundred and ninety five (85%) children have an isolated, single suture craniosynostosis. Only 9% of children have a diagnosis of a recognised craniofacial syndrome, including Muencke syndrome, (7 children), Saethre–Chotzen syndrome, (5 children), Crouzon syndrome (2 children), Pfeiffer syndrome (2 children), Antley–Bixler syndrome (1 child), Beare–Stevenson syndrome (1 child), Jacobsen syndrome (1 child) and Diamond–Blackfan Anaemia (1 child). Four children had no clear syndromic diagnosis, miscellaneous chromosomal anomalies or VACTERL sequence. Seven children were born severely premature, which was thought to contribute to the diagnosis (hypoxic-ischaemic injury, shunting, etc.). The demographic data of the children are summarised in Table 1.

There are 118 children (52%) diagnosed with a sagittal synostosis. Eighty-nine of these children had an isolated sagittal synostosis (75%). The demographic data of the children with sagittal synostosis are summarised in Table 2.

Data from at least one obstetric scan were obtained for 89 of the 118 pregnancies in which the child was diagnosed with a sagittal synostosis (75%), and data from two scans were obtained for 28 patients (24%). Morphology scans were available for 82 pregnancies (69%) and growth scans in 37 pregnancies (31%). The majority of pregnancies did not have any formal ultrasound scans after 20 weeks.

Table 1: Demographic data of children diagnosed with craniosynostosis born in SA/NT 2000–2014.

	Number of fetuses (%)	Isolated craniosynostosis	Multiple synostoses	Recognised craniofacial syndrome
Male	141 (62)	123	18	10
Female	88 (38)	72	16	11
Total	229 (100)	195	35	21

Table 2: Demographic data of children diagnosed with sagittal synostosis born in SA/NT 2000–2014.

	Number of fetuses (%)	Isolated sagittal synostosis	Multiple synostoses	Recognised craniofacial syndrome
Male	82 (69)	60	12	7
Female	36 (31)	29	7	2
Total	118 (100)	89	19	9

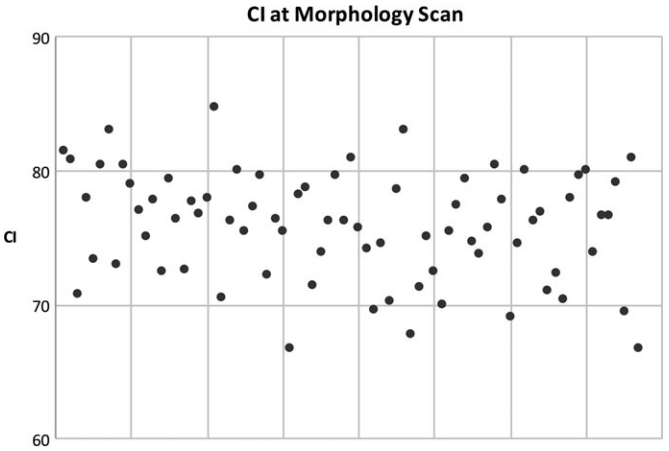

Figure 1: Distribution of the cephalic index (CI) of fetuses who developed sagittal synostosis. These measurements were obtained at the routine morphology scan performed between 17 and 22 weeks gestation. The mean CI was 76.

The CI was calculated from the morphology scan for 80 fetuses who developed sagittal synostosis (Figure 1). Twenty-six fetuses (33%) had a CI below the normal range. The mean CI was 76 (67–85), standard deviation (SD) = 4. The CI was calculated in the third trimester for 36 fetuses who developed sagittal synostosis (Figure 2). Seventeen fetuses (47%) had a CI outside of the normal range. The mean CI was 75 (63–85), SD = 5.

Scans in both the second and third trimesters were available for 28 fetuses who developed sagittal synostosis. Eight fetuses (29%) had a significant reduction in CI (>3) between the morphology and growth scans. The mean change in CI was −1 (range −13 to 9).

The group of children with isolated sagittal synostosis were also examined (78 fetuses). The CI was below the normal range in 24 of 78 (31%) of available scans in the second trimester and in 15 of 28 (54%) of available scans in the third trimester. Twenty-one fetuses had scans available from both second and third trimesters. The CI reduced significantly between second and third trimesters in eight (33%) fetuses. The mean change in CI was −2 (range −13 to 9).

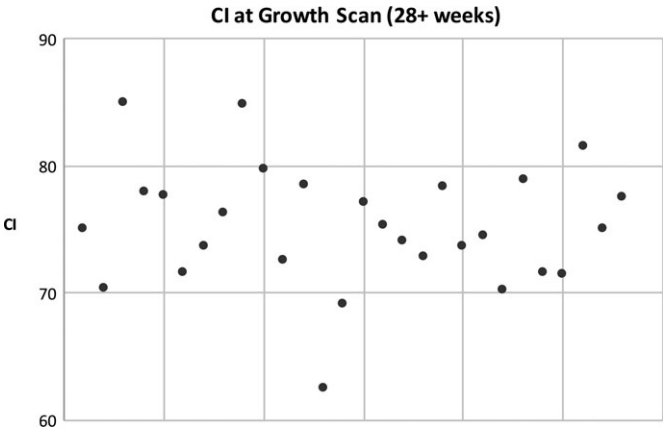

Figure 2: Distribution of the cephalic index (CI) of fetuses who developed sagittal synostosis. These measurements were obtained at third trimester growth scan performed after 26 weeks gestation. The gestation for each fetus varied, as the scans were performed for a variety of clinical indications. The mean CI was 75.

A diagnosis of craniosynostosis was suspected antenatally in only 7 of the 168 cases with imaging available for review (4.8%). Five of these cases were syndromal with multiple sutural fusions confirmed postnatally. One case had metopic synostosis and polyhydramnios, and the other case had an isolated sagittal synostosis. In a further five cases (3%), a comment was made about an unusual fetal head shape in the ultrasound report, but this was dismissed or not followed up. One case of Crouzon syndrome was diagnosed via chromosome analysis (mother also affected), but the head shape was normal on ultrasound.

On retrospective review of the available antenatal imaging, the diagnosis of sagittal synostosis is strongly suggested in several cases. A progressive reduction in CI indicating progressive scaphocephaly in late pregnancy has been demonstrated in a number of cases. In all these cases, the CI in the late third trimester was below 75.

Case 1 (Figure 3)

Thirty-year-old woman: The morphology scan showed a normal fetus with both BPD and HC on the mean and a CI of 81. A growth scan at 26+ weeks showed the HC to being growing along the mean, but the BPD now on the 5th percentile. The head shape is clearly more scaphocephalic and the CI has reduced to 74. The child was delivered by emergency caesarean section due to breech presentation in labour.

Case 2 (Figure 4)

Thirty-six-year-old woman: The morphology scan showed a normal 22-week fetus with a BPD and HC close to the mean. The CI was calculated at 78. A growth scan at 32 and again at 37 weeks shows progressive scaphocephaly, with the HC remaining on the mean and the BPD dropping below the 5th percentile. The CI at 37 weeks had reduced to 68. The child was delivered by emergency caesarean section for fetal distress due to prolonged labour without progression.

Case 3 (Figure 5)

Twenty-one-year-old woman with Crouzon syndrome: The morphology scan performed in a rural centre showed a normal fetus at 19 weeks. The head shape was mildly dolichocephalic, but well within the normal range. Serial growth scans were performed showing progressive scaphocephaly with a reduction in CI from 76 at 30 weeks, to a CI of 74 at 32 weeks and to a CI of 72 at 38 weeks. The child was delivered by emergency caesarean section due to cephalopelvic disproportion (CPD). The boy was diagnosed with Crouzon syndrome postnatally and had only a sagittal synostosis at birth.

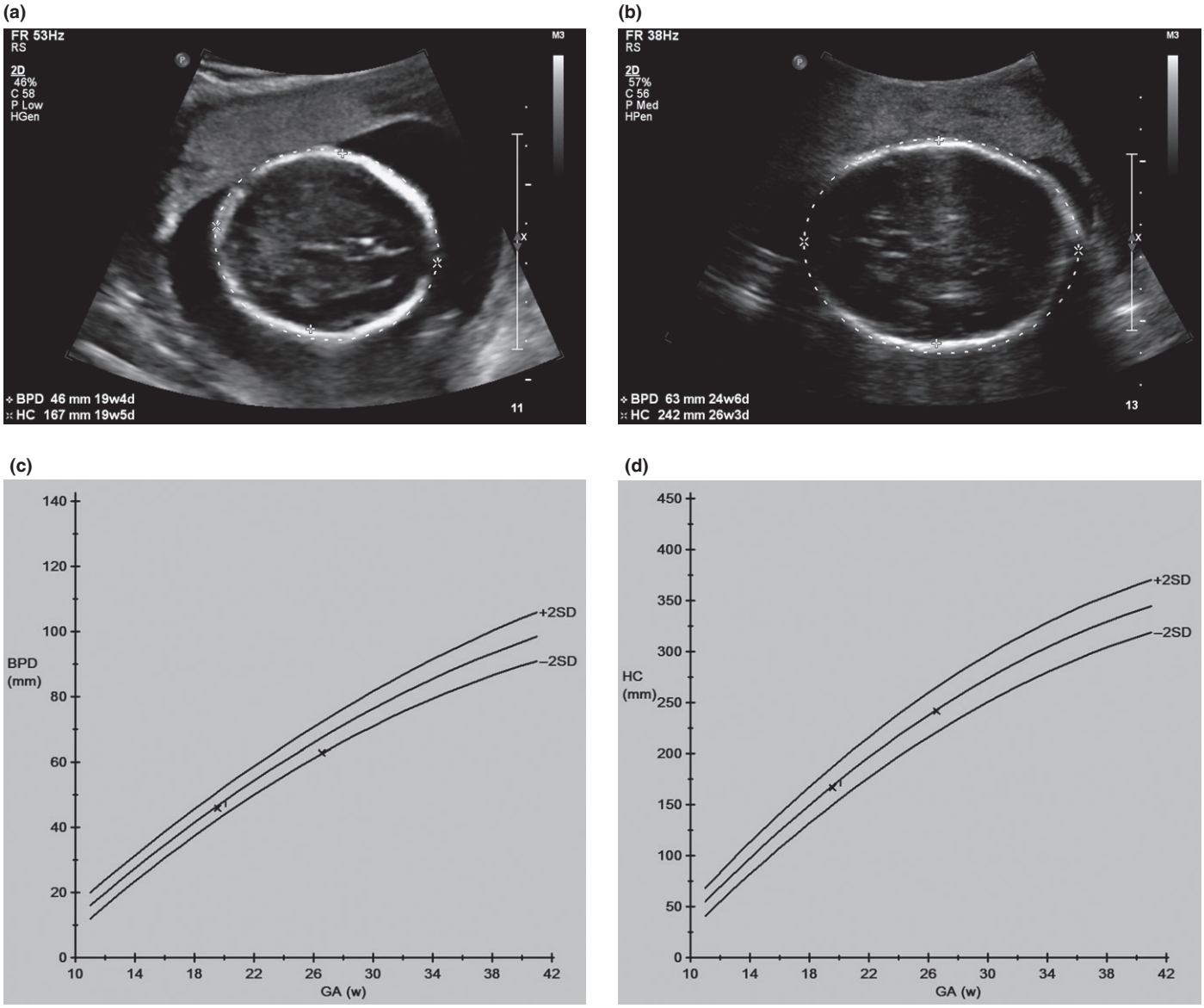

Figure 3: Scans performed during a pregnancy in a 30-year-old woman. (a) Axial cranial image and measurements at the morphology scan. (b) Axial cranial image and measurements at 27 weeks. (c) Graphic representation of the biparietal diameter (BPD) measurements, showing a drop in growth from the 50th to the 5th percentile. (d) Graphic representation of the head circumference (HC) measurements, showing appropriate head growth along the 50th percentile. The axial images show the fetal head becoming more dolichocephalic as the pregnancy progressed. This is confirmed by the stable growth of the HC, but dropping growth of the BPD.

The mode of delivery for those diagnosed with sagittal synostosis was also recorded. Infants born prematurely (earlier than 36 weeks' gestation) were excluded from analysis. A total of 112 pregnancies were included. The pattern of delivery is listed in Table 3. The data were compared with the total population data in SA over the same time period, provided by The Pregnancy Outcome (Statistics) Unit, SA Health (Table 4).

There was an increase in the number of emergency caesarean deliveries in women whose fetuses had sagittal synostosis when compared with the general population (21% vs. 17%). There were also a higher number of emergency caesarean sections performed for CPD and failure to progress in the study group compared with the general population.

There were 15 fetuses who had a CI of under 75 at the third trimester scan. Four of these fetuses (27%) were breech presentation at term. A further four fetuses (27%) were delivered by emergency caesarean section for CPD. Only two fetuses (13%) were born vaginally without grade 3 or 4 perineal or vaginal tears to the mother.

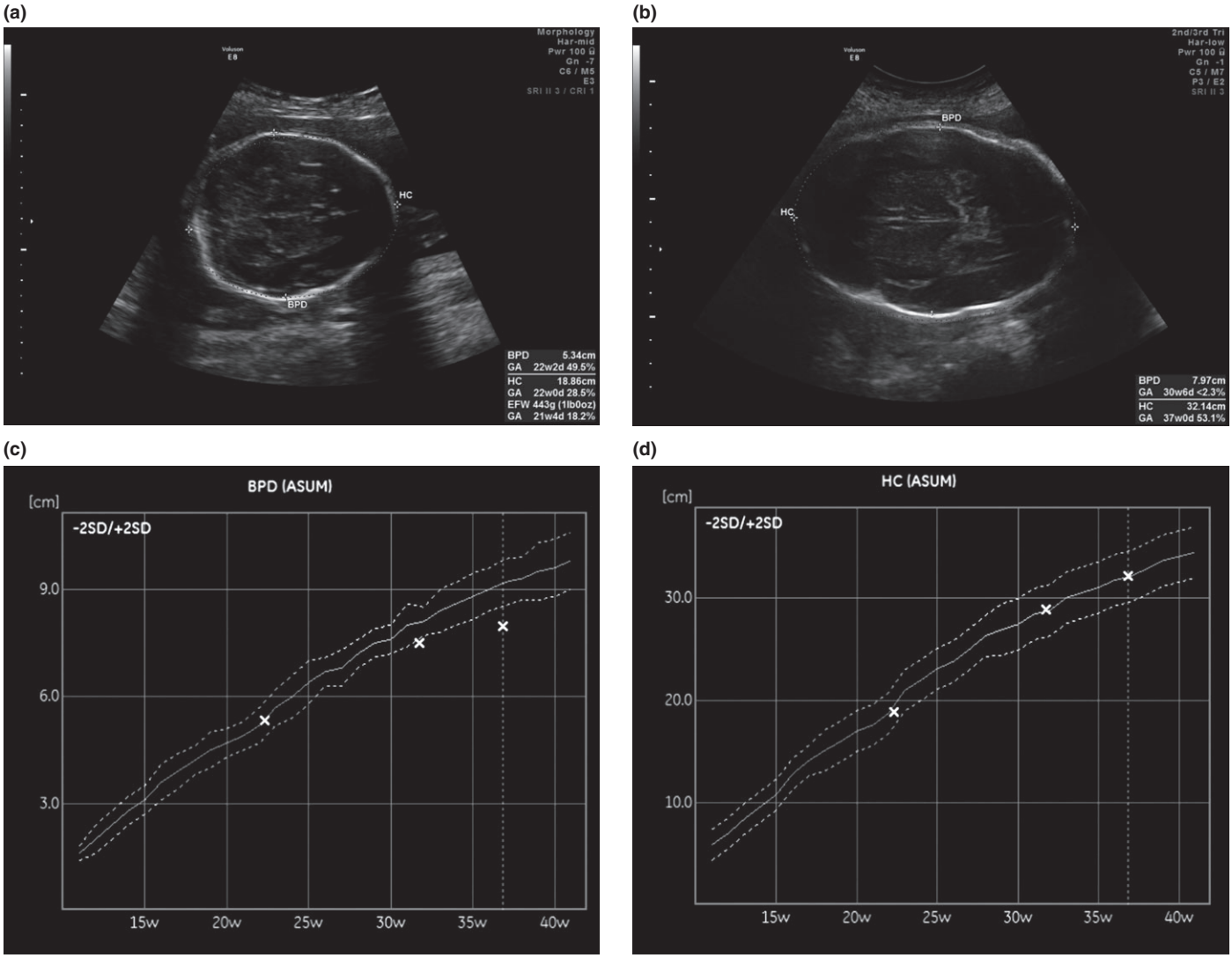

Figure 4: Scans performed during a pregnancy in a 36-year-old woman. (a) Axial cranial image and measurements at the morphology scan. (b) Axial cranial image and measurements at 37 weeks. (c) Graphic representation of the biparietal diameter (BPD) measurements, showing a progressive drop in growth from the 50th to the 5th to below the 2nd percentile. (d) Graphic representation of the head circumference (HC) measurements, showing appropriate head growth along the 50th percentile. The axial images show the fetal head becoming more dolichocephalic as the pregnancy progressed. This is confirmed by the stable growth of the HC, but progressive drop in growth of the BPD.

We have also been able to identify the cranial sutures with three-dimensional (3D) ultrasound in the second and early third trimester. The open sutures and anterior fontanelle are clearly seen in this normal fetus (Figure 6a), while in this 20-week fetus subsequently diagnosed with Pfeiffer syndrome, global craniosynostosis is obvious (Figure 6b).

Discussion

Craniosynostosis is under diagnosed antenatally. The largest study to date found only 10.8% of affected children were diagnosed or even had mention of an abnormal skull shape on antenatal ultrasound.[3] The numbers in our group were even lower (7.8%), and many of these had syndromic diagnoses where abnormalities of the face and limbs contributed to the diagnosis. There have been a small number of studies evaluating the cranial sutures on antenatal ultrasound, and these studies have universally found that the sutures are best seen on 3D ultrasound and the sagittal suture is the most difficult to identify.[8–11] It is only in the last 10 years that 3D ultrasound has become available, but this requires special ultrasound probes and highly skilled sonographers to obtain good images, which are still not

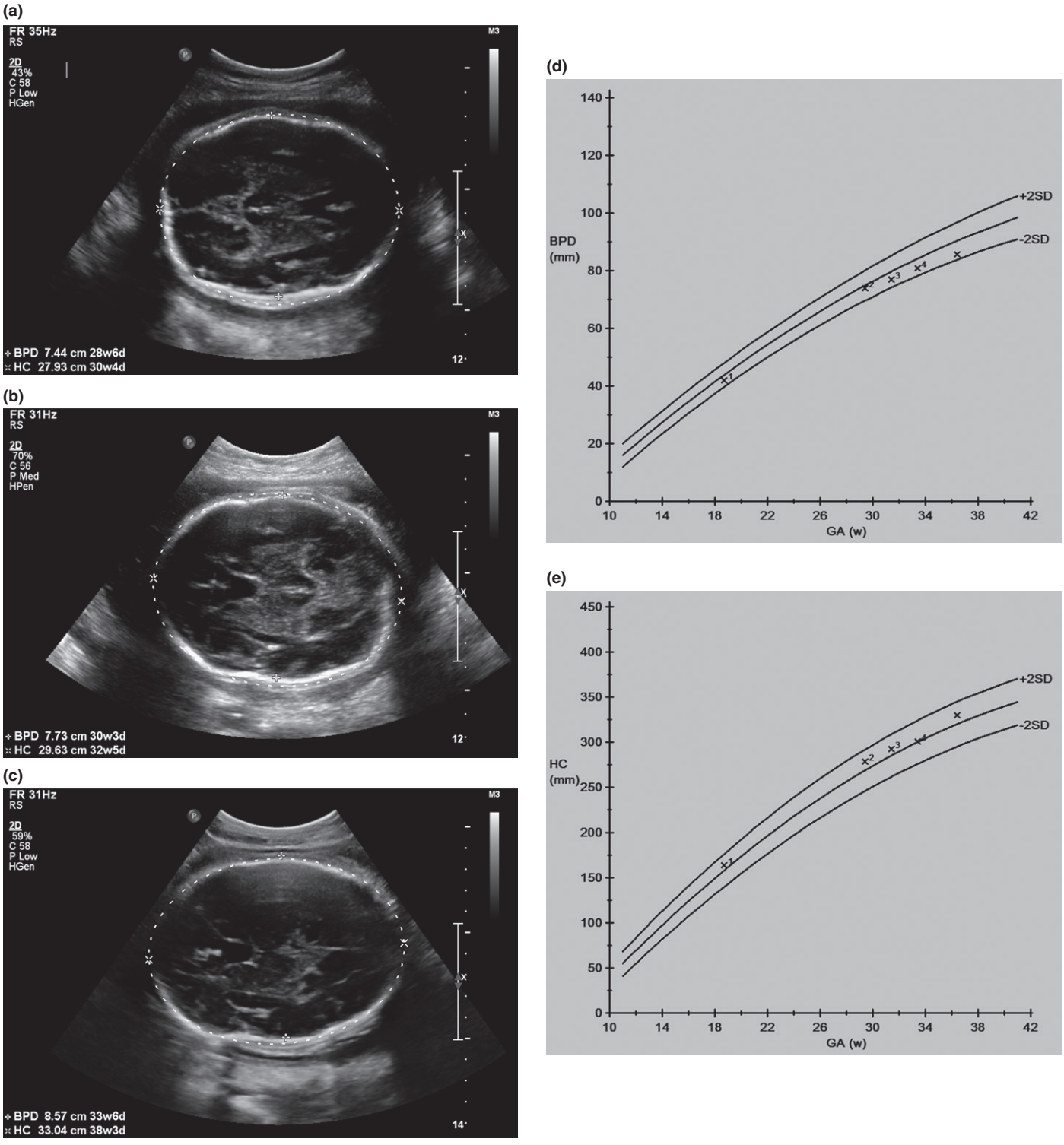

Figure 5: Scans performed during a pregnancy in a 21-year-old woman with Crouzon syndrome. (a) Axial cranial image and measurements at 29 weeks. (b) Axial cranial image and measurements at 31 weeks. (c) Axial cranial image and measurements at 35 weeks. (d) Graphic representation of the biparietal diameter (BPD) measurements, showing a gradual drop in growth from the 40th to the 10th percentile. (e) Graphic representation of the head circumference (HC) measurements, showing appropriate head growth along the 60th percentile. The axial images show the fetal head becoming more dolichocephalic as the pregnancy progressed. This is confirmed by the stable growth of the HC, but progressive drop in growth of the BPD. The diagnosis of Crouzon syndrome was confirmed post-natally.

Table 3: Method of delivery of term infants with sagittal synostosis in SA/NT 2000–2014.

Delivery type	Number (n = 112)	Per cent
Vaginal	51	46
Elective section	31	28
Emergency section	25	22
Unknown	5	4

Table 4: Delivery statistics for infants with sagittal synostosis compared with the population data in SA.[a]

	Study group (%)	Population (%)
Emergency section	22	17
Failure to progress, CPD	61	50
Breech at term	6	12
3rd/4th tears	2	2

[a] The Pregnancy Outcome (Statistics) Unit, SA Health. Data from 1 January 2000 to 31 December 2014.

available in many smaller centres due to the costs involved. 3D scanning is also time consuming in many cases, which prohibits its routine use in many centres.

The causes and timing of onset of craniosynostosis is still not clear. There have been suggestions made that fetal constraint may play a role in some cases,[5,12] and a number of genes have been identified as being involved, especially in syndromic cases. The cause is almost certainly multifactorial. The time of onset is also likely to be variable, which may explain our observation of a very large change in CI in some affected fetuses, and very little change in others. The data examining the stability of the CI antenatally is quite old and fairly sparse, and more research is needed in the area. Jeanty *et al.*,[6] Hadlock *et al.*,[7] and Mador *et al.*,[13] found the cranial index remains stable in the second and third trimester, whereas Kurmanavicius *et al.*,[14] and Gray *et al.*,[15] found significant variation with gestational age. The latter two studies, however, were both cross-sectional in design, whereas the Jeanty study[6] was longitudinal in nature producing more reliable results.

The CI was outside the normal range in a significant number of our patients. In many cases, this was not recognised, as the CI is not routinely calculated at antenatal scanning. Our data suggest that a CI outside the normal range, especially in the third trimester, should prompt careful evaluation of the cranial sutures, and consideration should be given to a further antenatal scanning late in the third trimester to re-examine the fetal skull and CI.

The article by Anderson *et al.*[4] was one of the first to raise concerns over maternal well-being from delivery of a child with

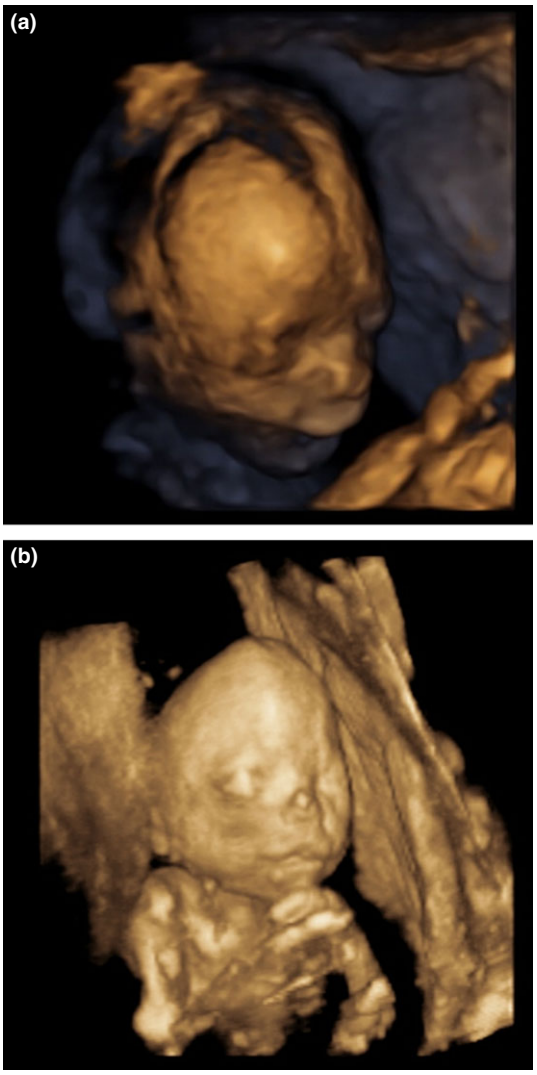

Figure 6: (a) 3D ultrasound image of a normal fetus at 20 weeks. The metopic, coronal and anterior sagittal sutures are clearly patent and well-demonstrated. (b) 3D ultrasound image in a 20-week fetus later diagnosed with Pfeiffer syndrome. The metopic and coronal sutures are fused in keeping with global craniosynostosis. This was confirmed at autopsy.

craniosynostosis. Four cases were reported where fetal craniosynostosis caused obstruction to labour, resulting in a significant perineal injury to the mother, and/or emergency caesarean section. Both Graham *et al.*[5] and Swanson *et al.*[16] noted a high incidence of CPD in their series, leading to a high frequency of emergency sections or forcep deliveries. They did not comment on any maternal pelvic injuries. Weber *et al.*[3] found the rate of perineal injuries was not significantly increased, but there was a significant increase in the number of vaginal tears compared with the general population. The rate of emergency section in this group was 17% higher than in the general population.

Weber *et al.*[3] also found significant concerns with fetal well-being in this group of infants as a result of these traumatic deliveries. Infants with craniosynostosis were four times more likely to need neonatal intensive care treatment than those not affected. Of great importance, they found those affected infants who were diagnosed antenatally and were delivered by caesarean section showed no major complications, whereas those delivered vaginally had cephalhaematomas in 16.7% of cases, dystocias occurred in 16.7% of cases and maternal perineal ruptures in one third of cases.

Cephalopelvic disproportion can be difficult to diagnose clinically by even the most experienced obstetrician.[17] Half of the emergency sections performed in SA are because of CPD, with a further 12% due to malpresentation [The Pregnancy Outcome (Statistics) Unit, SA Health]. Higher rates of malpresentation, including breech presentation, have been reported in fetuses later diagnosed with craniosynostosis.[3] A number of our group also had emergency sections for CPD and malpresentation, and a number were also delivered by planned section for breech presentation.

To our knowledge, the observation of a serial reduction in CI during pregnancy as detected by ultrasound scanning has not previously been reported. While this was not a feature seen in every case of sagittal synostosis, our cases resulted in emergency caesarean deliveries for malpresentation and/or obstructed labour. Recognition of this feature antenatally could prevent this situation by planning an elective caesarean section. The calculation of the CI is not routinely performed or reported in many Australian institutions. Most ultrasound machines can produce this calculation automatically at any obstetric scan with minimal programming.

Conclusion

Our data suggest that craniosynostosis could be diagnosed antenatally in a significant number of cases. The routine calculation of CI can be performed at antenatal scanning, and a value outside the normal range, or a change in CI during the pregnancy should prompt detailed scanning of the fetal skull and cranial sutures, including 3D scanning. An increase in antenatal diagnosis will enable better delivery planning for this group of patients, which should lead to a decrease in fetal and maternal morbidity as a result of obstructed labour.

Authorship

All three authors have contributed to the preparation of this article. The content, including images, has been agreed upon, and all authors have agreed on the final paper being submitted to the *Australasian Journal of Ultrasound in Medicine*.

Disclosure

No financial support was provided for this study. The authors do not have any conflicts of interest to declare.

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The Normal Fetal Cephalic Index in the Second and Third Trimesters of Pregnancy

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Abstract: The cephalic index (CI) is used in the evaluation of individuals with craniosynostosis. There is little agreement as to the normal range and stability of the CI during the fetal period, partly due to limited literature. We sought to determine the range, distribution and stability of the fetal CI in the second half of pregnancy. We also aimed to identify any relationship to delivery complications such as obstructed labor and malpresentation.

The fetal head circumference, biparietal diameter (BPD) and occipitofrontal diameter (OFD) measurements were obtained from standard ultrasound images. Each of 4304 fetuses had measurements taken at morphology scan performed between 17 and 22 weeks' gestation, and at growth scanning at 28 to 33 weeks' gestation. The cephalic index was calculated using the formula: CI = BPD/OFD × 100. The distribution of the CI at both scans is very close to a normal distribution. The mean CI at 17 to 22 weeks was 75.9 (SD, 3.7); the mean CI at 28 to 33 weeks was 77.8 (SD, 3.5). The mean change in CI was 1.9 (SD, 4.28), which is not statistically significantly different from zero ($t = 0.656$, $P = 0.512$, 95% confidence interval). No relationship was found between the CI in normal fetuses and delivery complications. There is a wide variation in the change in CI in the third trimester. A value below the normal range in the third trimester or a progressive reduction in CI during the latter half of pregnancy should provoke detailed scanning of the fetal cranial sutures to check for craniosynostosis.

Key Words: pregnancy, fetus, skull, biometry, ultrasonography

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The cephalic index (CI) is the ratio of the biparietal diameter (BPD) to the occipitofrontal diameter (OFD). It is used in the evaluation and planning of surgical procedures in individuals with craniofacial abnormalities, in particular craniosynostosis. The CI is not used as a routine antenatal ultrasound parameter in many centers. There are few studies published that have evaluated the normal fetal CI. One early study by Hadlock et al[1] found the normal fetal CI was 78.3 (SD, 4.4) and was stable across the range of gestational ages. Jeanty et al[2] collected longitudinal data in a small group of pregnancies and found a mean CI of 80.64 (SD, 4.97), using the now standard "inner-to-outer" measurement of BPD. Gray et al[3] collected single measurements on a large sample of fetuses, and through regression analysis concluded that the CI was variable depending on the gestational age of the fetus. The first large, cross-sectional study in the modern ultrasound era that included the CI in normal fetuses was published by Kurmanavicius et al.[4] In the development of normal ranges for fetal biometry, they found similar results to Gray et al,[3] in that the CI was variable across the gestations. Two further cross-sectional studies by Mador et al[5] and Nagesh et al[6] found conflicting evidence relating to the stability of the CI during pregnancy. Hence, there is little agreement as to the normal range, nor stability of the CI during the fetal period.

The diagnosis of craniosynostosis can be difficult antenatally. In syndromic craniosynostosis, the skull is often very abnormal and there may be associated limb abnormalities. Diagnosis is improving in single-suture synostoses with the introduction of 3D and 4D ultrasound, and the "Brain Shadowing Sign" was recently described by Krajden Hartz et al.[7] Isolated sagittal synostosis is particularly difficult to identify antenatally, yet there are studies reporting obstructed labor with these fetuses[8–10] due to the inability of the fetal head to mold during delivery, and higher rates of neonatal complications postdelivery.[11] The cranial measurements at midtrimester morphology scanning alone are of minimal value,[12] but a continual reduction in the CI through the third trimester has been identified as a pattern in sagittal synostosis.[13,14]

The primary aim of this study was to determine the normal range of the CI in the second half of pregnancy. The secondary aims were to evaluate the stability of the CI in the fetus during pregnancy and determine any relationship between the CI and presentation at delivery in normal fetuses. This could help with the identification of fetuses with isolated sagittal craniosynostosis in the future.

METHODS

Ethics approval was obtained from the following, all of which waived consent: Women's and Children's Health Network Human Research Ethics Committee, South Australia, University

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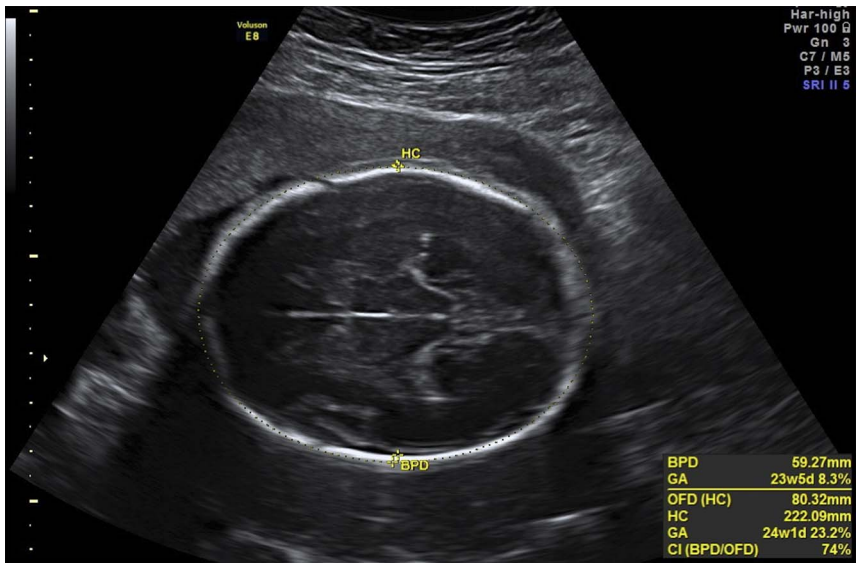

FIGURE 1. Normal fetal ultrasound image showing the standard cranial measurements performed in this study.

of Adelaide Human Research Ethics Committee, South Australia. Flinders Medical Centre Human Research Ethics Committee, South Australia, and the Department of Health and Menzies School of Health Research Human Research Ethics Committee, Northern Territory, Australia.

Participants were identified from the Radiology Information System at the Women's and Children's Hospital (WCH) in South Australia. Data was collected retrospectively from patients who attended between January 2011 and July 2016 for a third trimester pregnancy ultrasound. The WCH is the main tertiary obstetric, neonatal and pediatric referral hospital for South Australia, the Northern Territory, northwestern Victoria and western New South Wales, servicing a population of around 2 million people.[15] Inclusion criteria for the study were as follows:

- Singleton pregnancy. Dichorionic pregnancies with demise of 1 fetus in the first trimester were included.
- Formal pregnancy ultrasound performed at WCH at 28 to 33 weeks, including standard fetal biometry.
- Morphology ultrasound performed at 17 to 22 weeks' gestation at WCH or another accredited imaging practice[16] with electronic images available for review.

Exclusion criteria were as follows:

- Any fetal anatomical abnormality identified antenatally. Fetuses with ultrasound markers that are not necessarily associated with an anatomical abnormality were not excluded. Markers that were not excluded include thickened nuchal fold, echogenic gut, echogenic intracardiac foci, mild fetal renal pelvis dilatation.
- Multiple pregnancies.
- Fetuses with diagnosed intrauterine growth restriction at or before 33 weeks' gestation.
- Fetuses with a known chromosomal abnormality or inherited condition, even if no anatomical abnormality was seen at morphology scan.

The fetal head circumference, BPD, and OFD measurements were obtained from the ultrasound images. When all 3 parameters were appropriately measured as part of the scan, these measurements were used (Fig. 1). Many scans did not include a direct OFD measurement, so this was measured electronically using the radiology software. The BPD was remeasured in these cases as a check for accuracy.

Each fetus had 2 sets of measurements taken, one at morphology scan performed between 17 and 22 weeks' gestation, and another at 28 to 33 weeks' gestation. Scans were analyzed for fetuses of 2 distinct gestational age groups. The age group of 17 to 22 weeks was selected as this is the typical timeframe in which a morphology (anatomy) scan is performed. The gestational age range of 28 to 33 weeks was selected because most

TABLE 1. Characteristics of Pregnant Women in the Study (N = 4304)

	Number	Percentage
Age at delivery, y	Mean, 31.4 y Range, 15.4–50.8 y	
Parity		
First delivery	1745	40.5%
Previous delivery	2559 Range, 0–12, 32 previous twins	59.5%
Diabetes		
Gestational	714	16.6%
Type 2	67	1.6%
Type 1	43	1.0%
Delivery		
Vaginal	2698	62.7%
Planned section*	811	18.8%
Emergency section†	795	18.5%

*A planned Cesarean section is performed before the onset of labor.
†An emergency Cesarean section is performed after the onset of labor.

TABLE 2. Characteristics of Infants in the Study (N = 4304)

	Number	Percentage
Gestation at birth		
Term (≥37 weeks)	3767	87.5%
Preterm (28–37 weeks)	537	12.5%
Sex		
Male	2177	50.6%
Female	2127	49.4%
Presentation at birth		
Cephalic	4031	93.7%
Breech	193	4.5%
Transverse	23	0.5%
Not recorded	57	1.3%
Fetal abnormalities not excluded from the study	66	1.5%
Cardiac defects (ASD, VSD, PDA, TGA, TOF, valvular stenoses)	24	
Birth trauma, no long term sequelae (cephalhaematomas, small extradural hemorrhage)	17	
Deafness	5	
Talipes	5	
Genitourinary anomalies	4	
Epilepsy, normal MRI, no developmental delay	3	
Gastrointestinal anomalies	3	
Congenital cataracts, glaucoma	2	
Hematological (Kawasaki disease, leukemia)	2	
Cystic fibrosis	1	

ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TGA, transposition of the great vessels; TOF, tetralogy of fallot; MRI, magnetic resonance imaging.

growth scans in normal pregnancies are requested during this period, often for follow-up of a low-lying placenta or growth in the setting of maternal diabetes. Fetuses of over 33 weeks' gestation were not included because the fetal head can sometimes be difficult to very accurately measure if positioned very low within the maternal pelvis.

The placental position, liquor volume, and fetal presentation were also recorded. The delivery details were recorded where possible, including the method of delivery and gestation at which delivery occurred. The reason for surgical delivery was also noted where possible. The infant was then followed up at 12 months of age, and the following exclusion criteria were then applied:

- Infants diagnosed with any craniofacial syndrome or significant craniofacial abnormality. Minor, isolated problems, such as ankyloglossia, were not excluded.
- Infants diagnosed with any neurological disorder, abnormalities on cranial MRI scans or developmental delay by 12 months of age.
- Infants diagnosed with any chromosomal abnormality or systemic syndrome.
- Infants who contracted meningitis or similar infections that affected their neurological development in the first 12 months of life.
- Fetal death in utero or before 12 months of age.
- Infants who could not be traced after delivery to check their health status at 12 months of age.

STATISTICAL ANALYSIS

All data manipulations and statistical analyses were performed in the statistical software R, v3.5.1.[17] Differences in mean CI between normal fetuses and those with anomalies, at the morphology and third-trimester scans, were assessed using the 2-sample *t*-test.

RESULTS

Data were obtained from scans in 4447 pregnancies. One hundred forty-three (3.2%) patients were secondarily excluded at the postnatal review, giving data on 4304 fetuses (Tables 1–3). Scans were analyzed for fetuses of 2 distinct gestational age groups. The BPD measurements were compared graphically with the population curves established by the Australasian Society for Ultrasound in Medicine (ASUM).[18] The data showed good correlation with the established data, indicating the study fetuses were representative of the normal population (Fig. 2).

The cephalic index (CI) was calculated using the formula: CI = BPD/OFD × 100. The results are summarized in Table 4. The distributions of the CI at both morphology and growth scan are very close to a normal distribution (see Supplemental Digital Content Figs. 1–4: Normal quantile plots (including 95% confidence envelopes) of the cephalic index at the midtrimester morphology scan (Appendix 1, http://links.lww.com/RUQ/A175),

TABLE 3. Patients Excluded From the Study at Postnatal Review (N = 143)

Abnormality	No. Infants	Conditions
Multiple	22	Chromosomal = 7 (5× Trisomy 21, 1× Turners, 1× chromosome 2 duplication), "dysmorphic" = 7, VACTERL syndrome = 2, arthrogryposis = 2, NF1 = 1, Krabbe disease = 1, Russel Silver syndrome = 1, FFD/fibular hemimelia = 1
Neurological	36	"developmental delay"/autism = 14, HIE/birth asphyxia injury = 5, microcephaly = 5, severe seizure disorders = 5, neonatal/congenital infection = 2, tethered cord = 2, caudal regression = 1, sacrococcygeal teratoma = 1, microphthalmia = 1
Craniofacial	14	8× craniosynostosis, 4× cleft palate, 2× Goldenhar
Fetal/neonatal death	17	IUFD = 14, NND = 3 (2× HIE, 1× SMA)
Lost to follow-up	54	Moved interstate/overseas

NF1, neurofibromatosis type 1; FFD, focal femoral deficiency; HIE, hypoxic ischemic injury; IUFD, intrauterine fetal death; NND, neonatal death; SMA, spinal muscular atrophy.

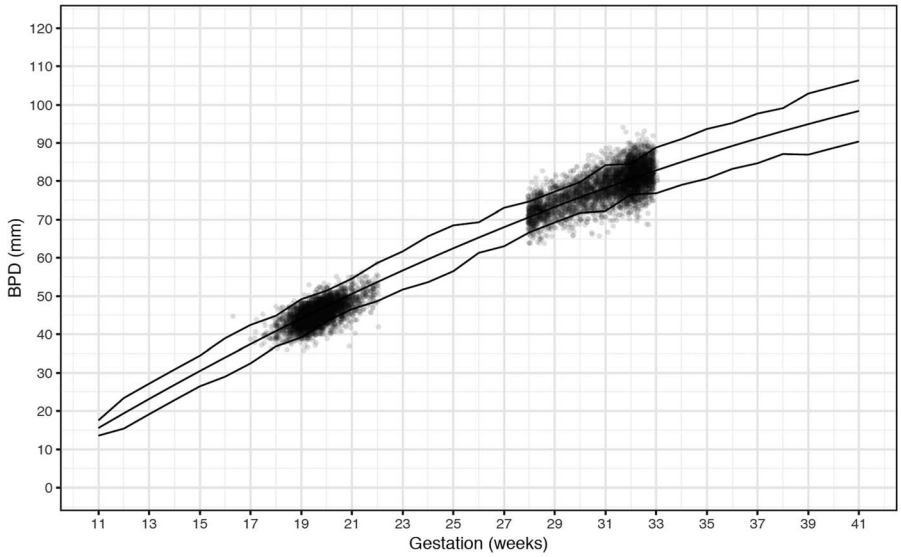

FIGURE 2. Scatter plot of the BPD at morphology and growth scan versus gestation age, including the ASUM average population curve. The center and ±2 SD line points have been 'jittered' horizontally to separate identical values.

and the third trimester growth scan (Appendix 2, http://links.lww.com/RUQ/A176) showing the distribution is very close to a normal distribution. Density plots of the cephalic index at midtrimester morphology scan (Appendix 3, http://links.lww.com/RUQ/A177), and at third trimester growth scan (Appendix 4, http://links.lww.com/RUQ/A178)). When analyzing the data from fetuses with abnormalities not excluded from the study, there is no significant change in the mean CI observed (Table 5) (morphology scans, $P = 0.127$; Fig. 3, third trimester scans $P = 0.407$; Fig. 4). The mean CI at 17 to 22 weeks was 75.9 (SD, 3.7), and the mean CI at 28 to 33 weeks was 77.8 (SD, 3.5).

The range of observed values for the CI at both morphology and growth scanning varies widely. Figure 5 shows a limited association between the 2 CI values, and the small correlation indicates the CI can change considerably between the 2 scans. The mean CI was slightly higher at 28 to 33 weeks than at 17–22 weeks and again followed a Normal distribution (see Supplemental Digital Content Fig. 5: Density plot of the change in cephalic index between the growth and morphology scans (Appendix 5, http://links.lww.com/RUQ/A179)). The mean change in CI was 1.9 (SD, 4.28), which is not statistically significantly different from zero ($t = 0.656$, $P = 0.512$, 95% confidence interval).

The time interval between scans in individual fetuses varied from just over 6 weeks to almost 16 weeks depending on the gestation at which each scan was performed. A linear regression analysis found that the increase in CI tends to be larger the further apart the 2 scans were (Fig. 6). For every additional week between the scans, the CI increased by 0.245 ($P < 0.001$). The large variability in the change in CI and the large sample size results in a very low coefficient of determination, indicating that less than 1% of the variability in the change in CI is due to the difference in gestational age.

There was little difference in the mean CI between fetuses that were in breech or transverse position at birth (Table 6). The mean CI was only slightly lower in these groups compared with fetuses in cephalic presentation (see Supplemental Digital Content, Figure 6: Box plots of the cephalic index at the growth scan. NA, information not available/not recorded [Appendix 6, http://links.lww.com/RUQ/A180]), which was significant only because of the large numbers of cephalic presentations compared with noncephalic ($P < 0.001$). There was also no significant

TABLE 4. Summary of the Cephalic Index During Morphology and Third Trimester Scans, and the Theoretical Normal Distribution With the Same Mean and Standard Deviation

	n	Mean	SD	2.5%	5%	10%	25%	50%	75%	90%	95%	97.5%
Normal morphology observed	4248	75.9	3.7	68.5	69.7	71.2	73.3	75.9	78.3	80.6	81.8	82.8
Normal distribution				68.6	69.7	71.1	73.4	75.9	78.4	80.7	82.0	83.2
Anomalies morphology observed	56	76.6	3.9	69.5	70.4	71.3	74.0	76.6	79.0	81.4	82.6	85.0
Normal distribution				69.1	70.3	71.7	74.0	76.6	79.2	81.6	83.0	84.2
Normal third trimester observed	4248	77.8	3.5	70.6	71.9	73.3	75.5	77.9	80.2	82.1	83.2	84.2
Normal distribution				71.0	72.0	73.3	75.4	77.8	80.1	82.2	83.5	84.6
Anomalies third trimester observed	56	78.2	4.1	70.5	71.1	73.4	75.1	78.3	81.3	82.9	83.9	85.7
Normal distribution				70.2	71.4	72.9	75.4	78.2	80.9	83.4	84.9	86.2

TABLE 5. Summary of the Change in Cephalic Index Between Growth and Morphology Scan, Including Sample Size (N), Mean, Standard Deviation, and Selected Percentiles for the Observed Data and the Theoretical Normal Distribution With the Same Mean and Standard Deviation for Normal and Not Normal Babies

	n	Mean	SD	2.5%	5%	10%	25%	50%	75%	90%	95%	97.5%
Normal observed	4248	1.90	4.28	−6.47	−5.15	−3.54	−0.86	1.85	4.67	7.36	8.97	10.28
Normal distribution				−6.48	−5.13	−3.58	−0.98	1.90	4.78	7.38	8.93	10.28
Anomalies observed	56	1.52	4.90	−9.41	−7.59	−5.74	−0.36	1.66	4.71	7.33	8.00	8.64
Normal distribution				−8.08	−6.53	−4.75	−1.78	1.52	4.83	7.80	9.58	11.12

difference in the mean CI of fetuses who mothers suffered third- or fourth-degree tears during delivery compared with those mothers who did not develop high degrees of perineal injuries (see Supplemental Digital Content Fig. 7: Box plots of the cephalic index at the growth scan versus the degree of perineal tearing recorded in the notes. NA, information not available/not recorded [Appendix 7, http://links.lww.com/RUQ/A181]). There was no relationship between the fetal CI and cases of obstructed labor ($P = 0.827$) (see Supplemental Digital Content Figure 8: Box plots of the cephalic index at the growth scan versus the delivery type (normal vaginal delivery versus emergency section for failure to progress or obstructed labor [Appendix 8, http://links.lww.com/RUQ/A182]).

DISCUSSION

This is the first large population-based study to investigate the fetal cephalic index in almost 2 decades. During this time, there have been significant advances in ultrasound technology with the introduction of 3D and 4D scanning on a routine basis. The cranial sutures can now be clearly imaged in the fetus, and cases of craniosynostosis can often be diagnosed antenatally.[7,13] Although an antenatal diagnosis of craniosynostosis does not alter the timing of surgical intervention, the reports in the literature of obstructed labor and increased complications arising from delivery make an antenatal diagnosis important.[8–11]

This study has established the normal fetal CI to be 75.9 (SD, 3.7) at 17 to 22 weeks' gestation. This is slightly smaller than some of the previous studies which can be attributed to several factors. The sample size was much larger than some of the early studies[1,2] and the standard BPD measurement based on ASUM criteria[18] (outer edge of the nearer parietal bone to the inner edge of the more distant parietal bone) was used, whereas other studies have used measurements from outer table to outer table[1] and including the fetal skin[4] which will increase the BPD values and therefore the CI. The normal fetal CI at 28 to 33 weeks has been established as 77.8 (SD, 3.5) which is close to that of the previous studies.[1,2,4]

The finding of large variability of the cephalic index in a normal fetal population supports the suggestion that isolated measurements of the fetal head of are of little use in diagnosing craniosynostosis.[12] This is particularly relevant to the head shape at midtrimester morphology scanning, where the skull is only partially ossified and therefore quite deformable. This study also found a large variability in the change in cephalic index during pregnancy (Table 4). Although the population average tends toward a slightly more brachycephalic fetal skull shape as pregnancy progresses, this is by no means universal. The mean change in CI from second to third trimester was 1.9, but the large standard deviation of 4.3 indicates a marked alteration in head shape in some normal fetuses. A cephalic index below the normal range in the third trimester should, however, prompt a more detailed scanning of the fetal cranial sutures, including 3D scanning to evaluate the sagittal suture and checking for a brain-shadowing sign.[7]

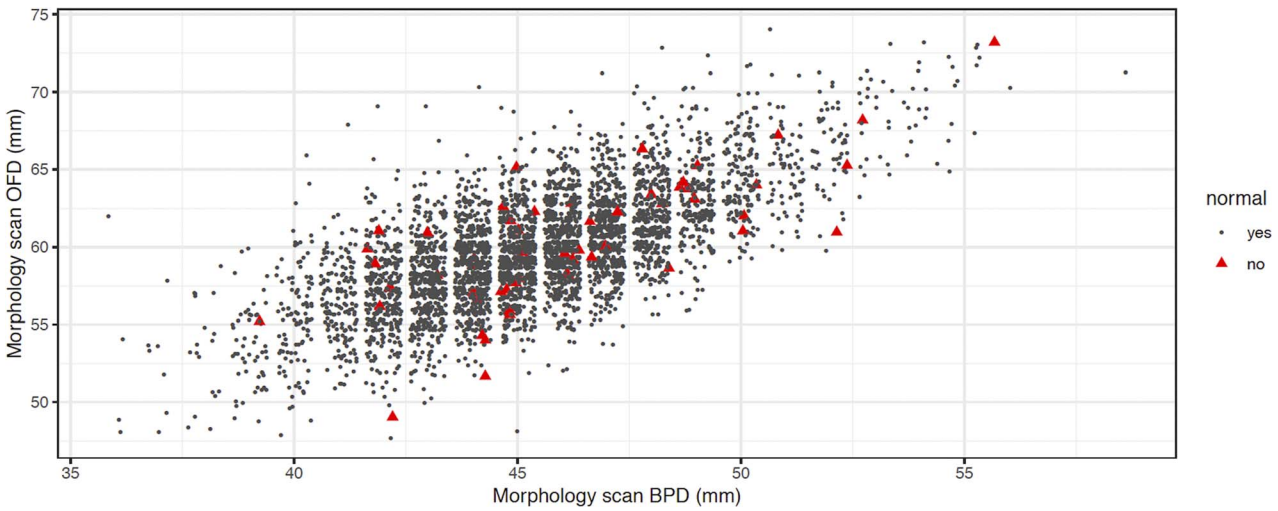

FIGURE 3. Scatter plot of OFD versus BPD at the morphology scan for normal (black dot) and not normal (red triangle) babies; points have been 'jittered' horizontally and vertically to separate identical values.

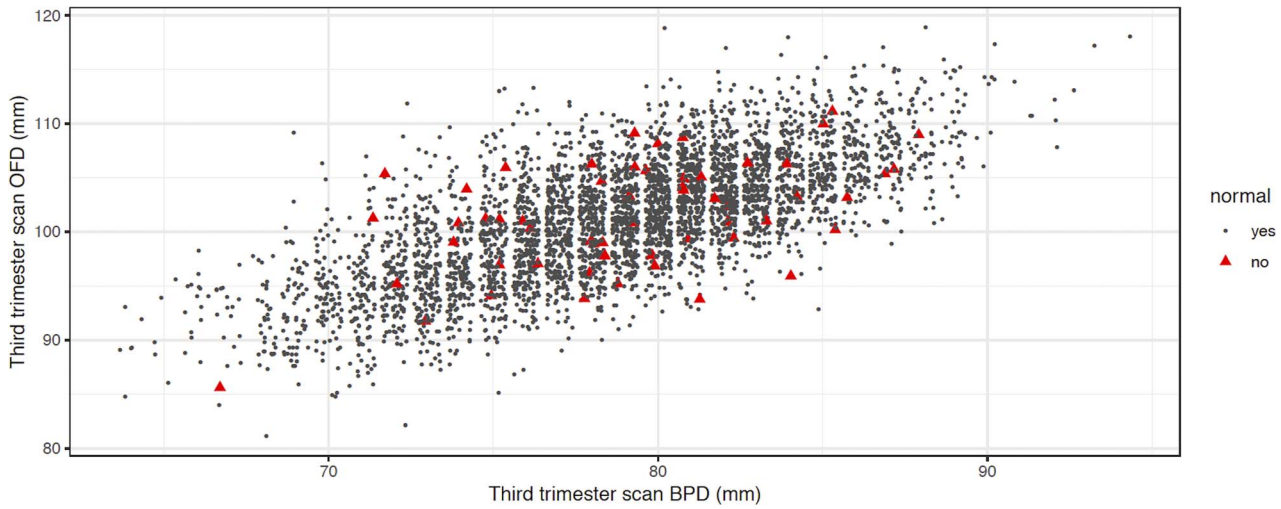

FIGURE 4. Scatter plot of OFD versus BPD at the growth scan for normal (black dot) and not normal (red triangle) babies; points have been 'jittered' horizontally and vertically to separate identical values.

The analysis of fetuses with anomalies not involving the skull or neural axis showed no statistically significant difference in the mean or normal range of the CI compared with completely normal fetuses. This is reassuring because one would not expect any major deviation from normal in this subgroup. The numbers in this subgroup were quite low representing 1.5% of all fetuses in the study. The quantile plots for both groups follow a normal distribution (see appendix).

The scans in fetuses of 2 distinct gestational age groups were analyzed. The time between scans was quite varied, from 6 to 16 weeks. The regression analysis shows that the change in fetal CI increases slightly, on average, with the time between scans. Although the change in CI during pregnancy was not statistically significant, it does equate with the finding that the CI typically increases with increasing gestational age, producing a slightly more brachycephalic skull shape.

Fetuses in cephalic presentation had a slightly higher CI than fetuses in breech or transverse position at delivery. The difference was statistically significant only due to the large number of cephalic presentations compared to non-cephalic presentations. Previous studies have also found a slightly more dolichocephalic skull shape in breech fetuses.[19,20] It has previously been hypothesized that the breech position was related to the development of craniosynostosis but there is little evidence for this. It is more likely that an abnormal skull shape in craniosynostosis predisposes the fetus to malpresentation as the head

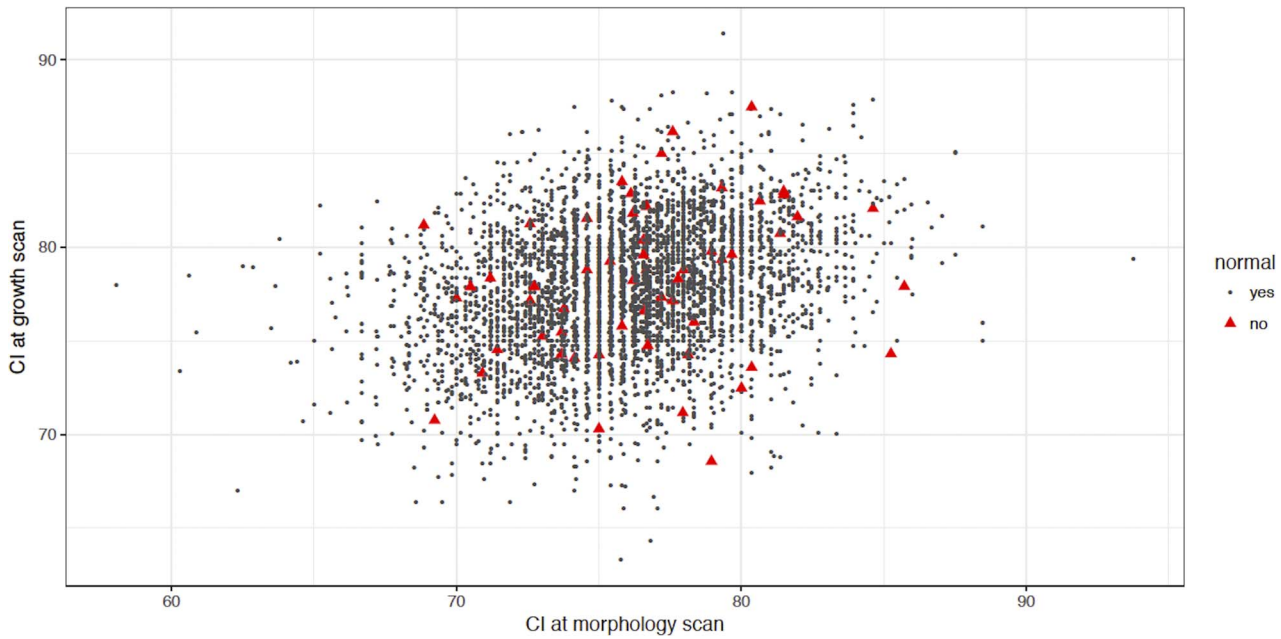

FIGURE 5. Scatter plot of the cephalic index at the growth scan versus the cephalic index at the morphology scan for normal (black dot) and not normal (red triangle) babies, showing little difference between the 2 groups.

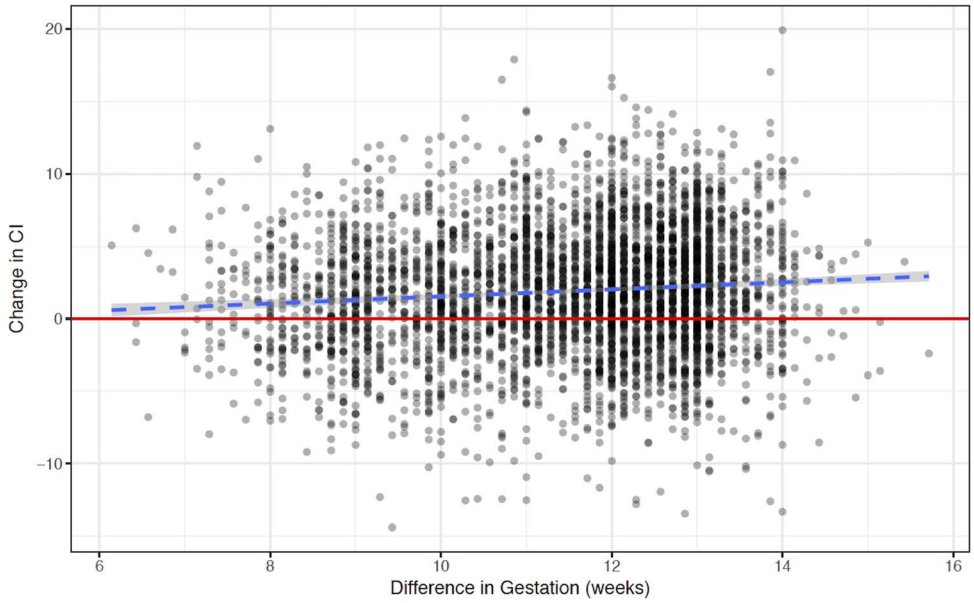

FIGURE 6. Scatter plot of the change in cephalic index between growth and morphology scans versus the corresponding change in gestation age; the blue dashed line shows the linear regression line; the red solid line is a reference line for zero change in CI.

cannot descend normally into the maternal pelvis. It is thought that the shape of the uterine fundus plays a role in the development of the "breech head."[19,20]

There was little difference in the fetal CI between those infants in cephalic presentation at delivery compared with those in breech or transverse position. There was also no association found between the fetal CI and maternal perineal injury nor fetal CI in fetuses delivered by emergency Cesarean section for obstructed labor or failure to progress compared with those delivered vaginally. This suggests that head shape alone is not a significant feature in obstructed deliveries of normal sized fetuses. This is not unexpected given that the head molds during delivery as long as the sutures are patent to allow this to occur.

CONCLUSIONS

The fetal CI is 75.9 (SD, 3.7) at 17 to 22 weeks' gestation, and 77.8 (SD 3.5) at 28 to 33 weeks' gestation in normal fetuses. The skull shape generally becomes more brachycephalic as pregnancy progresses, but there is a wide variation in the change in CI in the third trimester. The CI is of minimal use as an isolated measurement, especially at the midtrimester morphology scan, but a value below the normal range in the third trimester (below 71), or a progress reduction in CI from the morphology scan into the third trimester should provoke detailed scanning of the fetal cranial sutures including 3D ultrasound techniques to identify the sagittal suture. This may help with the identification of fetuses with isolated sagittal craniosynostosis antenatally to assist the obstetrician with delivery planning. In normal fetuses, there is no statistically significant relationship between the fetal CI, fetal position or obstructed labor.

TABLE 6. Mean Cephalic Index in Fetuses Related to the Presentation at Delivery

Birth Presentation	n (%)	Mean Cephalic Index
Cephalic	4031 (93.7)	77.87
Breech	193 (4.5)	76.01
Transverse	23 (0.5)	77.12
Not recorded	57 (1.3)	—

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The Prenatal Detection of Isolated Fetal Sagittal Craniosynostosis May Assist with Delivery Planning.

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Manuscript ID	Draft
Manuscript Type:	Original Manuscript
Keywords:	craniosynostosis, perinatal complication, fetus, skull, ultrasonography

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Short Title: Prenatal Detection of Sagittal Craniosynostosis

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Abstract

Background: The antenatal diagnosis of sagittal craniosynostosis can be challenging, but there are several published papers describing traumatic outcome to both the affected fetus and the mother during delivery of a scaphocephalic child. The antenatal imaging from affected children was collected along with the mother's obstetric history.

Aims: The aim of this study was to identify antenatal ultrasound features that may assist the diagnosis of sagittal synostosis before birth, to enable appropriate delivery planning and avoid both maternal and fetal trauma during birth.

Materials and Methods: Antenatal ultrasound scans in both the second and third trimesters were traced for 36 children with sagittal synostosis.

Results: The affected group showed a statistically significant reduction in cephalic index during the second half of pregnancy compared with the normal population which became slightly more brachycephalic ($p = 0.001$). There was also a much higher rate of malpresentation and surgical deliveries in the affected group than the normal population. There was a relationship between sagittal craniosynostosis and breech presentation and an associated higher rate of surgical deliveries.

Conclusion: It is possible to detect sagittal synostosis in the third trimester of pregnancy which may assist with delivery planning.

Introduction

Sagittal craniosynostosis is the most common isolated premature sutural fusion, affecting around one in every 5 000 live births[1]. The condition is usually diagnosed in the first year of life, with the child's head shape being noticeably scaphocephalic. The treatment is cranial vault reshaping done early in the child's life to obtain a normal cranial shape, and prevent complications which include raised intracranial pressure. Craniosynostosis is rarely diagnosed antenatally, and usually only when there are multiple sutural fusions as part of a syndrome, which may include associated limb anomalies.

There are an increasing number of reports in the literature describing maternal and fetal birth trauma where children are later diagnosed with craniosynostosis[1-6]. Antenatal diagnosis remains difficult, as the fetal head is deformable due to the open fontanelles and patent sutures. The resulting deformability creates significant variability in the normal fetal head shape, but suture function is critical for delivery as the fetal skull needs to mould to permit passage through the maternal pelvis.

The age of onset of sutural fusion remains uncertain in craniosynostosis[7]. Only multi-sutural syndromic forms are able to be reliably diagnosed at the mid-trimester morphology scan. In current Australian obstetric practice, not all pregnancies undergo an ultrasound scan in the third trimester. There is now strong evidence that the clinical diagnosis of intrauterine growth restriction in the third trimester is unreliable[8-12], and growth scanning may become routine in late pregnancy within a short time period. This may provide an opportunity to detect craniosynostosis prior to delivery. A progressive reduction in fetal cephalic index (CI) and deflection in the biparietal diameter (BPD) curve have been described previously as indicators of sagittal synostosis[5, 6]. The normal fetal CI in the second half of pregnancy has recently been confirmed[13].

This information may assist in the recognition of unusually scaphocephalic fetal skulls in those undergoing scanning in the third trimester.

The aim of this study was to compare the antenatal ultrasound imaging between affected and non-affected children to identify features that may assist with the antenatal diagnosis of sagittal synostosis. This may help identify affected fetuses in the future, to assist with delivery planning. We also compared our cohort of children diagnosed with sagittal synostosis with the background population to determine if there are differences relating to childbirth between the two groups.

Materials and Methods

Ethics approval was obtained for this retrospective study from the <BLINDED FOR REVIEW>, both of which waived consent. Children born in South Australia (SA) or the Northern Territory (NT) since January 1, 2000 with a diagnosis of sagittal craniosynostosis were identified through the <BLINDED FOR REVIEW> and the Radiology Information System of the <BLINDED FOR REVIEW> in SA. The antenatal ultrasound scans and delivery details were collected where available. All available scans were electronically archived, many earlier scans were only produced in hard copy format and were therefore not available. The BPD, occipitofrontal diameter (OFD) and head circumference (HC) were measured and the CI calculated for each scan via the equation: CI = 100 x BPD/OFD. Measurements used were performed either at the time of ultrasound scanning, or retrospectively using computer software to obtain accurate measurements from the original imaging data. All ultrasound scans were performed at accredited imaging practices by qualified sonographers, and included standard fetal biometry consistent with the Australian Society of Ultrasound in Medicine Guidelines[14].

The data obtained were compared with the local population data obtained from the Pregnancy Outcomes Unit, SA Health (Pregnancy Outcomes in South Australia (2003 – 2015)[15], the NT

Government, Department of Health (NT Midwives' Collection, Mothers and Babies 2003 – 15)[16] and the Fetal Cephalic Index Study[13].

All data analyses were performed in the statistical software R v.3.5.2 (R Core Team, 2018). Associations between the sagittal synostosis group and the population with respect to gender, delivery, and presentation were investigated using two-way tables and the Chi-squared test, using Monte Carlo simulated P-values[17] using 2000 'replicates'. As population statistics were only presented one variable at a time, regrettably, more complex analyses, taking into account more than one variable, were not possible.

The change in CI between growth and morphology scans was calculated for normal fetuses[13] and those with sagittal synostosis. The difference in average CI between the two groups was assessed at each scan using Welch's t-test, as was the average change in CI. In addition, a linear regression, taking into account the temporal separation between the second and third trimester scans, was fitted to the change in CI, allowing for differences between the two groups.

Results

129 children were born in SA/NT between 2000 and 2018 that have come to the attention of the <BLINDED FOR REVIEW> with isolated sagittal synostosis. Of those 129 children, seven were diagnosed as syndromic and were excluded from further analysis.

The details of the birth of the children with sagittal synostosis was collected and compared with the normal population. The data are summarized in Supplementary Table 1. The median gestational age for delivery was 39 weeks' gestation (range 24 – 42 weeks, gestation unknown in two cases). This is very similar to the general population[15-27, 43]. There is a statistically significant difference between the deliveries for the two groups, due to the higher rate of Caesarean

deliveries and the lower rate of unassisted vaginal deliveries in the sagittal synostosis group (χ^2 = 20.1, p = 0.001). This is demonstrated in Figure 1. There was also a statistically significant difference between the presentation at delivery between the babies with sagittal synostosis and the normal population (χ^2 = 13.0, p = 0.003). There were a lower number of vertex presentations amongst the babies with sagittal synostosis (Figure 2).

Serious perineal tears (third and fourth degree) were recorded in 3.8% of vaginal deliveries of infants later diagnosed with sagittal synostosis compared with 2.7% of vaginal deliveries in the population. There was no statistically significant difference in relative occurrence of tears associated with the delivery of an infant later diagnosed with sagittal synostosis compared with the normal population (χ^2 = 0.25, p = 0.65).

Second trimester morphology ultrasound scans were traced for 91 children (74.6%) and third trimester growth scans were performed in 36 pregnancies (29.5%). Fifteen of these children (41.7%) had multiple third trimester scans during pregnancy – only the scan closest to 32 weeks was used for this study. Scans in both trimesters were available in 28 pregnancies (23.0%).

The mean CI at morphology scan was 76.0 (standard deviation (SD) 4.3) and at growth scan was 74.5 (SD 4.5) (Supplementary Table 2). This compares to a mean CI in the normal population of 75.9 (SD 3.7) at morphology scan and 77.8 (SD 3.5) at growth scan. The difference in mean CI was not statistically significant (p = 0.77) at the morphology scan but was statistically significantly different at the growth scan (p = 0.001). Where both scans were available, the average change in CI between the second and third trimester scans in fetuses with sagittal synostosis was -1.6 (SD 5.0). There is a statistically significant difference between the change in CI of the babies with sagittal synostosis compared with the normal population, who showed an average change in CI of +1.9, SD 4.3 (p = 0.001). This is shown in Figure 3, which shows the density curves of the change in

CI between the two scans for the two groups of fetuses. A linear regression analysis was performed, as there was some variability in the time period between the second and third trimester scans in both the normal population[13] and the sagittal synostosis group. This is shown in Figure 4, which shows a scatter plot of the change in CI versus time difference between scans for both groups, including the least squares regression lines. From this plot it is evident that the change in CI in sagittal synostosis fetuses is more likely to be negative compared with the normal population[13], that is, the head shape is more likely to become more scaphocephalic than the normal population which tends to become slightly more brachycephalic, although this effect tends to reduce the further the scans are apart. The two regression lines are statistically significantly different, both in intercept ($p < 0.001$ at 12 weeks separation between scans) and gradient ($p = 0.02$).

Discussion

The findings of a significantly higher rate of Caesarean sections amongst the sagittal synostosis group is consistent with the previous studies. 50.8% of affected children in the study were delivered by Caesarean section compared with a rate of 32.3% in the background population. This is much higher than the rates reported by Weber et al[3] (26% vs 24%) and Swanson et al[4] (33% vs 24%) who examined all craniosynostoses, and Heliovaara et al[1] (31% vs 17%) and Cornelissen et al[6] (28% vs 12%) who looked only at sagittal synostosis. There were more than double the proportion of breech presentations in the study group (11.5%) compared with the background population (4.7%). This is similar to the study by Weber et al[3] (12% vs 5.4%), although the Swanson et al[4] and Cornelissen et al[6] studies reported lower rates of breech presentation (5.8% and 3%). The sagittal synostosis group had a higher rate of both elective and emergency Caesarean sections than the background population, but especially elective Caesarean sections. This may be due to the higher

incidence of breech presentations, although in both the study and background population groups there are often multiple reasons given for a surgical delivery.

The reported rate of serious (third and fourth degree) perineal tears was not statistically significantly higher in mothers who deliver infants later diagnosed with sagittal synostosis. The limited ability of the scaphocephalic head to mould normally during delivery and the increased rate of malpresentation may be leading to more Caesarean sections deliveries, and thus the rate of serious perineal tears is not elevated as might be expected. Previous studies have reported an increase in vaginal tearing[3] in pregnancies of children later diagnosed with sagittal synostosis.

The "breech head" was first reported by Haberkern et al[18]. They noted scaphocephaly in infants with breech presentation and commented on the potential for birth injury during vaginal delivery. None of the affected infants had craniosynostosis diagnosed post-natally. Kasby and Poll[19] also noted the "breech head" in at least one third of breech babies, and commented on the reduced CI in this group. The raises an interesting question in the sagittal synostosis population: How does the presence of scaphocephaly relate to a breech presentation? It is likely that in many cases the elongated fetal head does not fit in the maternal pelvis, with a breech presentation allowing the fetus to descend in the later weeks of pregnancy. The evidence for the "breech head" along with other studies into the possibility of fetal constraint as a contributing factor in the development of non-syndromic craniosynostosis[20-22] neither prove nor disprove that the breech presentation may play a role in the development of sagittal synostosis, but warrants further investigation.

The mean CI in the sagittal synostosis group was not significantly different from that of the normal population at second trimester morphology scan. This has two important implications in craniosynostosis diagnosis. Firstly, the morphology scan alone is of no value in the diagnosis of sagittal craniosynostosis. The lack of a difference in the CI between the two groups on a single

scan gives no indication that a sutural fusion may be present. Secondly, the lack of any difference in CI between the two groups at morphology scan, but a statistically significant difference at third trimester growth scan suggests that in the majority of affected fetuses, the sutural fusion occurs in the third trimester or later. It has been shown previously that a progressive reduction in the growth of the BPD compared with the HC is often seen in the second half of pregnancy in affected fetuses[5, 23]. (Figure 5).

It has been reported that the onset of craniosynostosis can be delayed and progressive[24, 25]. Fusion may be pre- or post-natal[1, 7], and the earlier the onset, the more significant the effect on skull shape[7]. An abnormal head shape is detected in 2 – 3% of pregnancies at routine anatomy scanning[26]. In a 2007 study, 72 fetuses with dolichocephaly at morphology ultrasound were followed, and none developed craniosynostosis[27]. Gray et al[28] found a wide variation in the normal CI during pregnancy, as did Kurmanavicius et al[29] and Constantine et al[13], who both examined a large number of normal fetuses. This contributes to the explanation as to why craniosynostosis is rarely diagnosed in the second trimester, unless there are other abnormalities present[3, 5, 26, 30].

The incidence of isolated sagittal synostosis is approximately one in 5000 live births[1] and while our data shows a higher rate of surgical deliveries in this group, many infants still deliver without incident. Our data does not support the use of 3D ultrasound scanning in every fetus with a reduced CI in the third trimester. It would be neither time nor cost effective when many normal fetuses have a low CI in the third trimester and the incidence of isolated craniosynostosis is low. However, if a progressive reduction in fetal CI is observed in the third trimester and a vaginal delivery is planned, 3D ultrasound scanning to visualize the sagittal suture could be of benefit to detect sutural fusion.

The main limitation of this study relates to the numbers in the sagittal synostosis group. Only a small number of affected children had multiple antenatal scans (as per obstetric practice at the time) to allow the CI to be calculated. There is also a discrepancy between the gender distribution in the sagittal synostosis group compared with the background population, with a male to female ratio of 2.2:1 compared with 1:1 in the background population. This is a reflection that sagittal synostosis is more common in males[1], which has been previously well-established. There were also differences in the methods of data collection and terminology relating to pregnancy and childbirth between SA and NT that made comparison with the study group difficult. However, NT only contributed 13% to the population data and hence any (minor?) differences in reporting methodology between the two jurisdictions are likely to have only a small effect. Where possible, stillbirths were excluded from the comparison data.

In summary, there is a clear relationship between the presence of sagittal craniosynostosis and breech presentation at delivery in affected fetuses. There is also a marked increase in the rate surgical deliveries in this group of infants. It is possible to diagnose sagittal synostosis in the third trimester by noting a progressive decrease in the fetal CI, which should provoke 3D scanning of the fetal skull to examine the sagittal suture. A breech presentation in the late third trimester should increase suspicion of sagittal synostosis when the other ultrasound markers are present.

Figure Legends

Figure 1. Bar chart comparing the method of delivery between the group with sagittal synostosis (SS) and the population (Pop).

Figure 2. Bar chart comparing the presentation at delivery between the group with sagittal synostosis (SS) and the population (Pop). Births where presentation is unknown have been excluded.

Figure 3. Density plots of the change in cephalic index between the morphology and growth scans for fetuses with sagittal synostosis (SS) compared with the normal population (Pop).

Figure 4. Scatter plot of the change in CI between the second and third trimester scans versus the corresponding difference in time between the scans. The grey dots represent the normal population (Pop) and the red triangles represent the fetuses with sagittal synostosis (SS). The dashed lines in corresponding colors represent the linear regression lines for the 2 groups.

Figure 5. Head circumference (HC) and biparietal diameter (BPD) plots and cranial images of another fetus that was diagnosed with sagittal synostosis after birth. The HC remains close to the same percentile throughout the third trimester, whereas the BPD growth drops off over the same time period.

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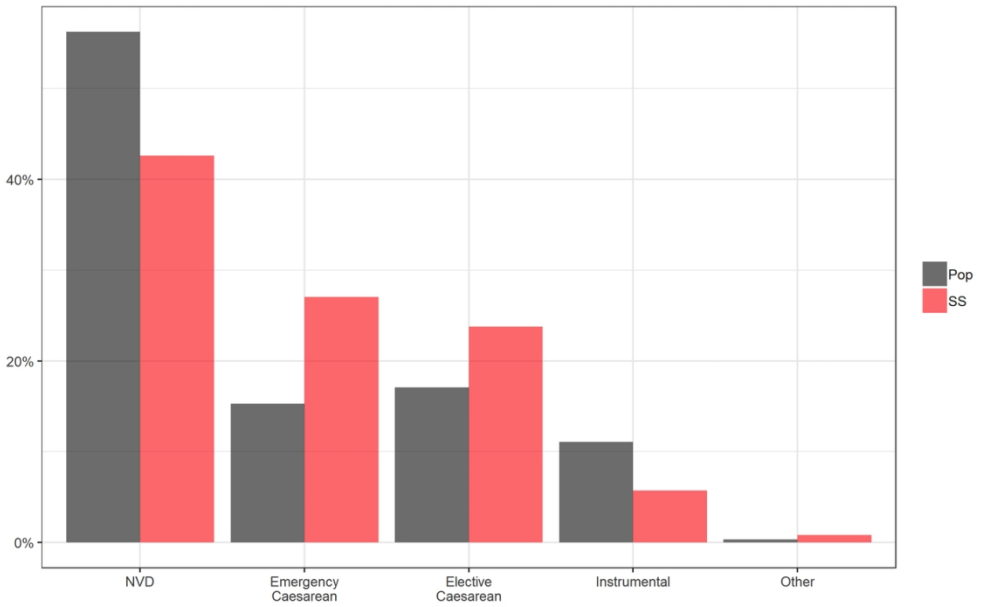

Figure 1. Bar chart comparing the method of delivery between the group with sagittal synostosis (SS) and the population (Pop).

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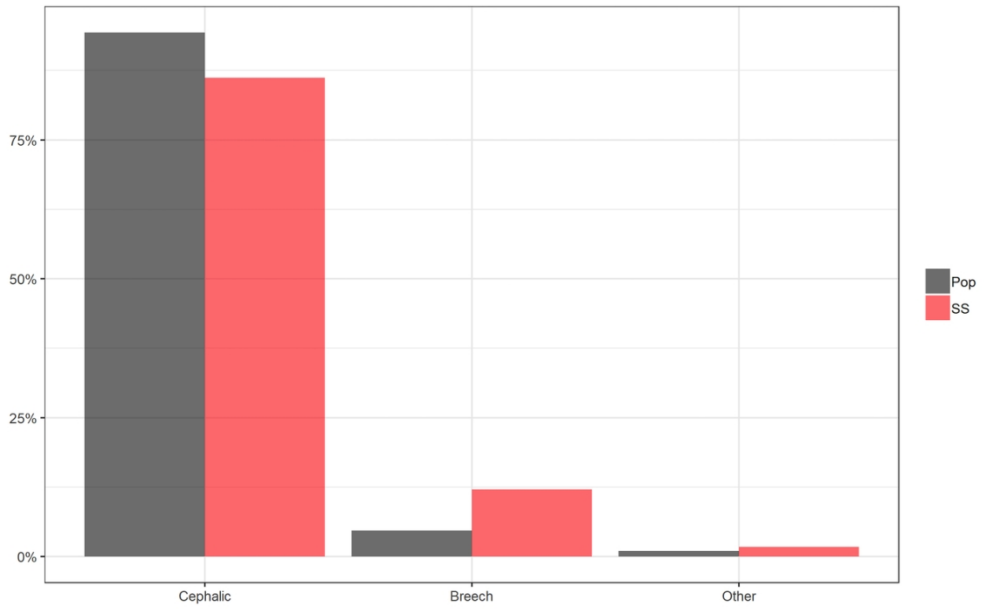

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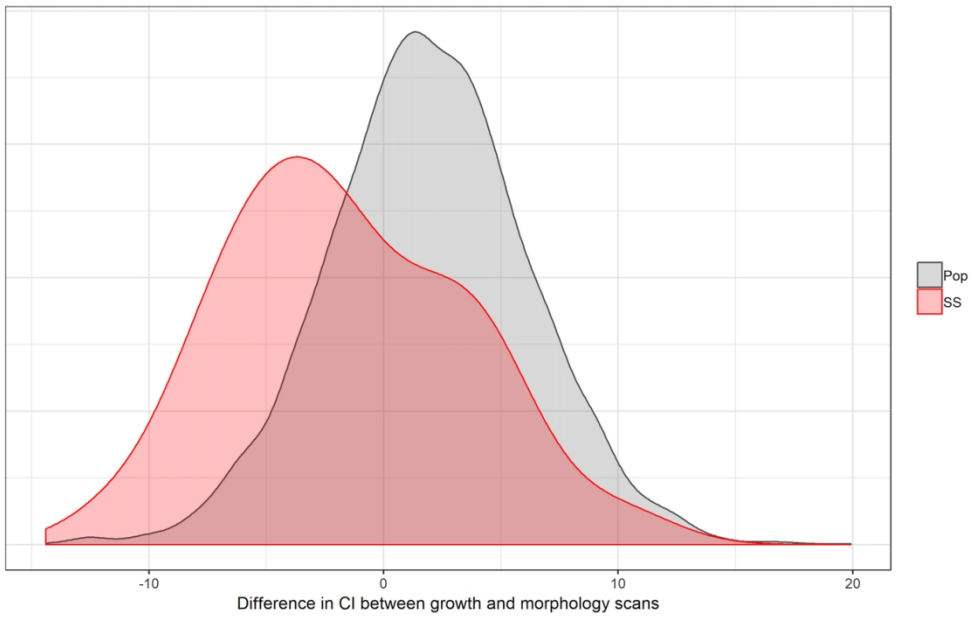

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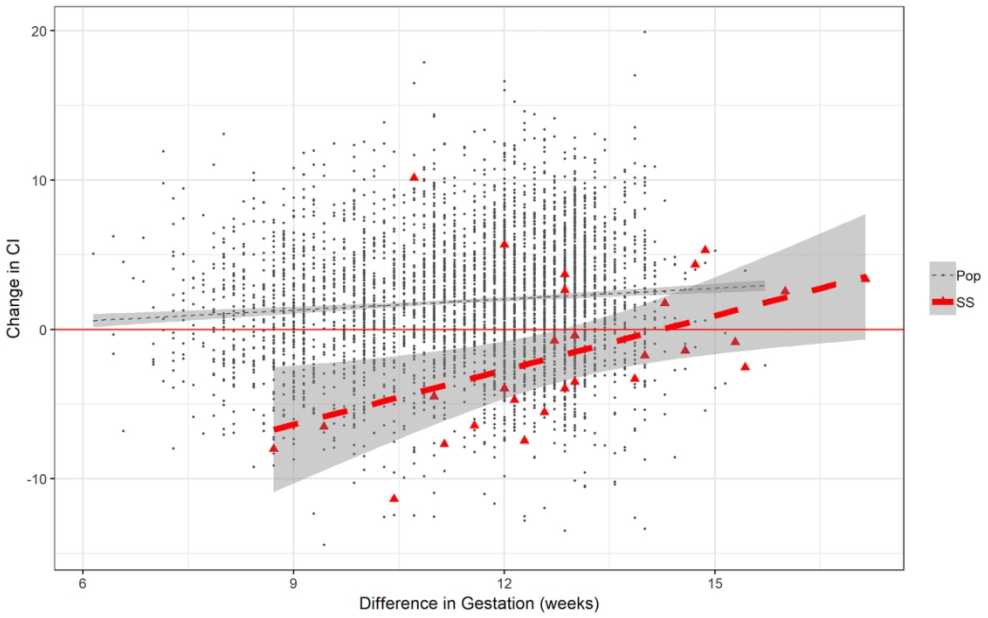

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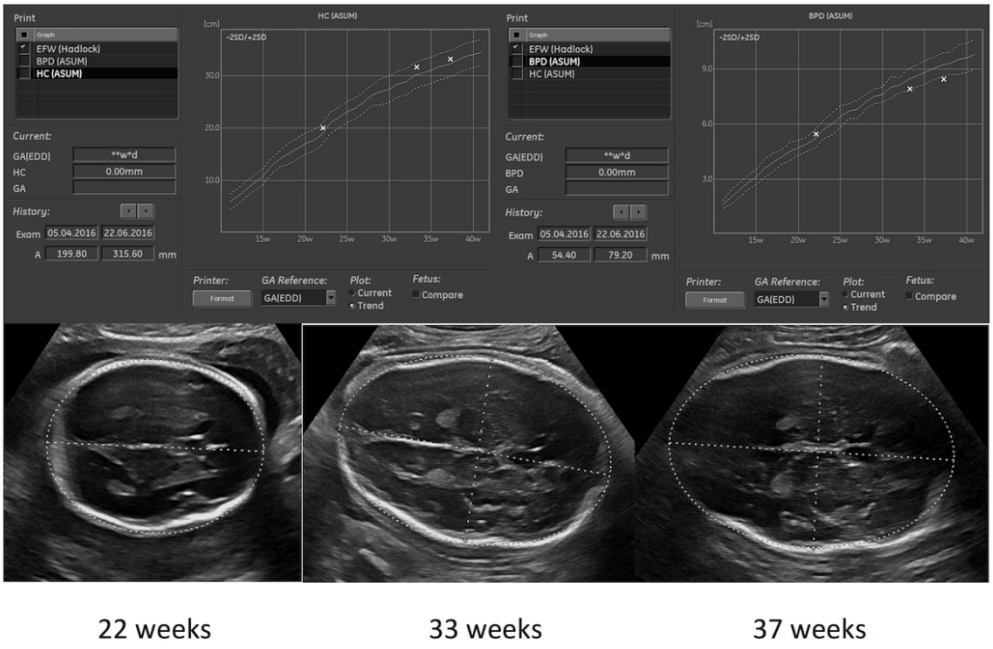

Figure 5. Head circumference (HC) and biparietal diameter (BPD) plots and cranial images of another fetus that was diagnosed with sagittal synostosis after birth. The HC remains close to the same percentile throughout the third trimester, whereas the BPD growth drops off over the same time period.

99x66mm (300 x 300 DPI)

Supplementary Table 1. Presentation and method of delivery for non-syndromic babies with sagittal synostosis compared with the population.

Number (%)	Vertex presentation	Breech presentation	Other eg transverse, compound, mobile	Normal vaginal delivery	Caesarean delivery	Elective section	Emergency section	Instrumental delivery	Other/unknown
Sagittal synostosis	106 (86.9)	14 (11.5)	2 (1.6)	52 (42.6)	62 (50.8)	33 (27.0)	27 (23.8)	7 (5.7)	1 (0.8)
SA/NT population 2003 – 2015[15, 16]	284782 (94.2)	14143 (4.7)	3497 (1.2)	167819 (56.2)	96524 (32.3)	45561 (15.3)	50963 (17.1)	33010 (11.1)	1037 (0.3)

Supplementary Table 2. Summary of the CI at the second and third trimester antenatal ultrasound scans (observed data) and the normal distribution for children diagnosed with sagittal craniosynostosis.

	n	Mean	SD	2.5%	5%	10%	25%	50%	75%	90%	95%	97.5%
2nd Trimester scan observed	91	76.0	4.3	66.9	69.5	70.2	73.2	76.4	78.8	81.0	82.2	84.9
2nd Trimester normal distribution				67.6	69.0	70.5	73.1	76.0	78.9	81.5	83.0	84.4
3rd Trimester scan observed	36	74.5	4.5	67.7	68.9	69.6	71.3	74.0	77.4	79.4	82.6	84.1
3rd Trimester normal distribution				65.6	67.1	68.7	71.5	74.5	77.6	80.4	82.0	83.4
Change in CI observed	28	-1.6	5.0	-9.1	-7.9	-7.5	-4.9	-2.1	2.6	4.6	5.5	7.1
Change in CI normal distribution				-11.5	-9.9	-8.1	-5.0	-1.6	1.8	4.8	6.7	8.2

Chapter Four

The antenatal diagnosis of craniosynostosis

Craniosynostosis, or the premature fusion of the cranial sutures, can affect any or all of the major and minor sutures of the skull. Isolated sagittal craniosynostosis one of the most important of the sutural fusions, firstly because it is the most common, and secondly because the fusion of the sagittal suture has a profound effect upon the ability of the fetal skull to mould during vaginal delivery. The sagittal suture is the longest of the cranial sutures and combined with the midline location, premature fusion of this suture has the most significant effect of the suture overlapping of the fetal skull which is necessary for a normal vaginal birth. The incidence of antenatal diagnosis of sagittal craniosynostosis is not known, but in our initial study we found only 7.8% of affected children had any suspicion of a craniosynostosis raised at antenatal ultrasound scanning[78], and Weber et al[79] found only 10.8% of all affected children had an abnormal head shape noticed at antenatal ultrasound scanning[79].

Surgery for craniosynostosis is performed for two main reasons. The first reason is physiological: a percentage of children with sutural fusions will develop raised intracranial pressure and surgery can increase the size of the cranial cavity to reduce this pressure. The second reason is cosmesis: to correct the abnormal head shape so the child does not look abnormally different from their peers. Surgery is typically performed in the first year of life when diagnosis is made appropriately early. There is currently no available antenatal treatment for the condition. There has been little research into the antenatal diagnosis of craniosynostosis, partly because the condition is uncommon, and partly because the treatment of the condition is

unaffected by an antenatal diagnosis. The sentinel paper on the importance of an antenatal diagnosis of the condition came from Anderson et al in 2005[80], who reported on a series of cases where infants diagnosed with craniosynostosis had difficult, prolonged or complicated deliveries due to obstructed labour. The outcomes for the infants was good in all cases, but the maternal outcomes were less satisfactory with some mothers suffering serious perineal disruption and requiring repair. This paper was followed by the Weber et al study in 2010[79], that reported higher rates of neonatal complications including neonatal intensive care admissions and respiratory problems in affected infants. Further papers have since added to our understanding that craniosynostosis is associated with a higher rate of delivery complications than the background population[81-83]. The need to diagnose this condition antenatally is now clear, but there are a number of barriers that currently prevent diagnosis from occurring.

The fetal skull is highly malleable, due to the fibrous sutures and fontanelles still present at the midtrimester anatomy scan. Anyone involved in antenatal ultrasound scanning has seen the fetal skull become temporarily "squashed" by a strong uterine contraction, and recover as the contraction settles. Populations across the globe have developed nomograms for the normal skull dimensions during pregnancy, which largely focus on the head circumference (HC) and biparietal diameter (BPD). The skull shape can be numerically assessed by means of the cephalic index (CI), which is the relationship between the BPD and the occipitofrontal diameter (OFD), however this measurement has not been particularly popular in recent years, due to the known deformability of the fetal skull. The ratio was not thought to be of particular significance antenatally and is predominantly used in the postnatal assessment of

cranial shape in surgical planning. Our initial study in 2016 showed a progressive reduction in the fetal CI during pregnancy is a marker of isolated sagittal synostosis[78]. One of the challenges this study raised was the lack of a nomogram for the normal fetal cephalic index during pregnancy. How can an abnormally low CI be reported if there is no predetermined normal range? A normal range is known post-natally and in childhood, but this cannot necessarily be extrapolated into the antenatal period.

The investigation of the normal fetal cephalic index was aiming to determine the normal range during the second half of pregnancy, and to examine the stability of the CI during pregnancy. Two early studies by Hadlock et al[84] and Jeanty et al[85] found conflicting results as to the stability of the CI during pregnancy, but had very different methodologies. The technology associated with ultrasound has progressed remarkably since the 1980s, and there have been some changes in the measurement guidelines. Kurmanavicius et al[86] revisited the CI in 1999, but there has been very little research in the literature in the past 20 years. We retrospectively evaluated ultrasound biometry in a large number of normal fetuses who had at least two scans during the second half of pregnancy. By comparing our data to the established biometry charts used in pregnancy we were able to determine our population was representative of the normal population.

The study produced two valuable findings. Firstly, we established the normal range for the fetal cephalic index in the second half of pregnancy. This now enables the CI in any individual fetus to be compared to the background population, and a determination made as to whether the CI is normal or abnormal. This will then assist is decision making with regards to further investigation of the skull shape. Three-

dimensional ultrasound scanning has been available for a number of years, but is very time consuming and requires considerable experience to perform well, which precludes its routine use at this point in time. An abnormal CI would be a good indication to perform this time-consuming and therefore expensive scan to visualise the cranial sutures.

Secondly, we found that the fetal head shape become slightly more brachycephalic as the pregnancy progresses through the third trimester. The increase in CI is small, but when compared to the progressive reduction in CI seen in fetuses with sagittal synostosis, the difference is significant[87]. We now have the basis for an antenatal diagnosis of sagittal craniosynostosis.

There were some significant short-comings in this diagnostic method. The largest is that only a proportion of pregnancies have an ultrasound scan in the third trimester. Most scans are currently done for suspected growth restriction or macrosomia, for threatened preterm labour or similar, or to check placental position. This means that many low risk pregnancies do not receive an ultrasound scan past 20 weeks' gestation. This is reflected in our population of infants with craniosynostosis, of which only one third had a third trimester scan[87]. However, with the increasing rate of obesity making clinical determination of fetal growth increasingly unreliable[88], and growing evidence that clinical diagnosis of growth restriction is difficult even in experienced hands[88-93], the trend towards routine third trimester growth scans is progressing. This will give the opportunity to detect a reduction in CI in the third trimester in most pregnancies, which will allow for more detailed 3D scanning in suspected cases of sagittal craniosynostosis.

Dissemination of this new information is another limitation in making an antenatal diagnosis of isolated sagittal synostosis. There are many, many medical journals focussing on the areas of obstetrics, ultrasound, imaging and fetal diagnosis in the English language and even more when other languages are considered. It is very difficult to disseminate new research to very large groups, especially when relating to a relatively uncommon condition. The "brain shadowing" sign was described by Krajden Haratz et al in 2016[94], but still remains largely unrecognised amongst many sonologists. This sign is the result of acoustic impedance of the fused cranial sutures producing abnormal shadowing across the brain that does not occur when the cranial sutures are patent. The reliability of this sign in the diagnosis of fetal craniosynostosis is not yet known.

Another potential issue is that there are many causes of obstructed labour and cephalopelvic disproportion (CPD). The cephalic index focuses solely on the fetal factors, that is, that an abnormal fetal head shape cannot necessarily pass through the maternal pelvis without causing injury to mother and/or child. The maternal pelvis also needs to be considered. The maternal pelvis can be a variety of shapes and the size of the pelvic inlet is critically important in the ability to deliver the fetal head[95]. Hence, there will be women who can deliver a scaphocephalic head without major difficulty. The incidence of CPD also reduces with increasing parity[96], so women in their first pregnancy are also at a higher risk than multiparous women. The cephalic index study is not designed to predict fetuses that may obstruct during delivery. Even in fetuses with known sagittal synostosis which may affect the ability of the fetal head to mould during vaginal delivery, the aim is to forewarn the treating obstetrician so

that appropriate delivery options can be discussed with the patient, and if the decision is a vaginal delivery, appropriate measures can be taken if the labour is not progressing as it should.

The effects of isolated fetal sagittal synostosis on childbirth need to be considered in both the mother and the child. Obstructed delivery can result in significant maternal morbidity, specifically through damage to the perineum and pelvic floor[96-98]. The fetus can be affected by hypoxia, nerve injury and fractures[96, 99-101]. These injuries in both mother and child can result in life-long disability and rarely, death. Death is thankfully uncommon in first world society, but the long term effects of obstructed labour can be significant in both mother and child, both physically and psychologically.

It was most interesting to note the difference in operative deliveries between the local population and the populations studied by Weber et al[79], Swanson et al[102], Heliovaara et al[81] and Cornelissen et al[82]. All studies found an increased incidence of Caesarean deliveries in the sagittal synostosis population compared with the general population, but the rate of operative deliveries in general was much higher in Australia than the other countries (Austria, USA, Finland, Netherlands, Sweden). Despite this difference, there was still a significantly higher rate of Caesarean deliveries of children with sagittal synostosis than those without. While Caesarean delivery is generally considered very safe, there is little doubt that vaginal deliveries are considered the safer option in most low-risk women[103-105]. Studies have considered factors such as maternal death, haemorrhage, sepsis, length of hospital stay and venous thromboembolism, but fewer consider the long term physical and

psychological impact of severe perineal injuries and the sequelae such as urinary or faecal incontinence, and ongoing pain and sexual dysfunction[106]. It is likely that many women would rather take the risks of a Caesarean section than the chronic disability that can occur from a high grade perineal injury. There is good evidence that a planned Caesarean delivery has better outcomes than an emergency Caesarean section[107, 108]. This is another potential benefit to mother and child if a diagnosis of sagittal synostosis can be made antenatally, giving the choice of a planned surgical delivery is desired.

Weber et al[79] were the first group to evaluate the effect of obstructed labour due to sagittal synostosis on the neonate. They found affected infants had a significantly higher rate of birth complications, including low Apgar scores, abnormal umbilical artery pH values, fetal hypoxia, primary resuscitation, and neonatal intensive care admissions. With the exception of intensive care admissions, these factors are all associated with a poorer outcome in the short or long term, or both[109-113]. There are other complications of obstructed delivery that have been reported in the literature, although not specifically as a result of craniosynostosis. These include pressure necrosis of the neonatal scalp[114], skull fracture and intracranial haemorrhage. Neonatal intensive care admissions can save lives, but at a significant financial cost, and if the infant has any permanent deficits, the lifetime expense can be substantial[115, 116]. It is clearly preferable for both the health of the infant and the financial impact on society and the health system to prevent as many birth complications as is possible.

While the psychological impact of obstructed labour and neonatal birth trauma is very difficult to quantitate, the financial cost is easier to evaluate. There is limited data available in Australia, but in the USA, the average cost per day of neonatal intensive care for an infant born at over 32 weeks of age is around US$1000[117]. Most data concentrates on very low birthweight infants, whereas those admitted for complications of obstructed labour are not. In the USA, lifetime costs for individuals with mental retardation were estimated at $51.2 billion US and $11.5 billion US for individuals with cerebral palsy[116]. When considering the United States has a population approximately ten times that of Australia with similar levels of medical care, the costs in Australia can be estimated at A$3.6 billion for people with mental retardation and A$0.8 billion for people with cerebral palsy. Australia had a gross domestic product of A$1.69 trillion in 2016, and spends more than 10% of this on health and medical care[26]. In 2014-15, Australia spent A$8 billion on disability support, which includes accommodation, respite, employment and access[118]. The healthcare of the disabled is included in the healthcare spend. Overall, lifelong disability has a very significant financial impact on Australian society. Every effort needs to be made to prevent lifelong disability to minimise this financial impact on society, as well as the physical and psychological impacts on the individual and their family.

The antenatal detection of sagittal craniosynostosis gives choices to the pregnant woman and her medical team. The decision to continue with a vaginal delivery can be made, with plans to change to a surgical delivery if labour is not progressing. A surgical delivery can be chosen, and there is strong evidence that a planned Caesarean delivery has fewer complications than an emergent Caesarean delivery[104,]

[107, 119]. Whatever the women and their healthcare providers decide, the knowledge that a sagittal synostosis is present in the infant can assist is preventing both neonatal and maternal injury, resulting in better outcomes for mother, child, and society as a whole through long term financial benefits.

Chapter Five

Summary

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There is little doubt that prevention is, indeed, better than cure in most healthcare settings. People are much happier and healthier if illness can be avoided or prevented, and this benefits the community in multiple financial ways, including a reduction in lost productivity as well as a significant reduction in health care costs. So many aspects of disease prevention can reduce not only personal suffering and inconvenience but also assist with maximising value for money with regards to health expenditure. Some of society's most simple interventions result in the most benefit to the population's health and the healthcare budget.

There are few interventions as beneficial as the fluoridation of the water supply, which at a cost of twenty six cents per person, can help preserve the dentition of an entire community[16]. Society ought to maximise all available resources to maintain the health of the population within a manageable budget. Utilisation of commonly performed imaging studies to prevent illness and injury outside the indication for which the imaging is initially performed will assist in preserving the health of the community while helping to manage health expenditure.

The CACO study showed that the identification of carotid artery calcification on routine dental panoramic x-rays can assist with stroke prevention[120], which is one of Western societies most common and costly permanently disabling afflictions[60].

The appropriate use of orthopantomography and CT scanning will increase diagnostic accuracy, minimise radiation exposure and minimise costs in the evaluation of maxillary sinus disease[121].

The development of a nomogram for the fetal cephalic index should increase the antenatal detection of sagittal craniosynostosis, which gives expectant mothers and their obstetricians delivery choices that may prevent both pelvic injury to the women and birth-related injury to the child that can have life-long consequences for both[78, 87, 122].

It is important that medicine and dentistry continue to utilise all possible aspects of diagnostic imaging to maximise the benefit to the individual patient, as well as minimise the financial cost to society. The above studies are all examples of how the clinical benefit to the patient can be maximised with minimal or no increase in the financial burden to society, and potentially cost saving in the long term through disease prevention. An ounce of prevention may well have been worth a pound of cure in Benjamin Franklin's era[1], but in the twenty first century, a few cents of prevention could be worth millions of dollars of cure, as well as a priceless amount of health and well-being to the individual.

Appendix

Published Papers

Constantine S, David D, Anderson P. The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better. Australasian Journal of Ultrasound in Medicine. 2016;19(3):91-8. DOI: 10.1002/ajum.12016.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Carotid Artery Calcification on Orthopantomograms (CACO Study) - is it indicative of carotid stenosis? Australian dental journal. 2019 Sep 14;64(March):4-10. DOI: 10.1111/adj.12651.

Constantine S, Clark B, Kiermeier A, Anderson PP. Panoramic radiography is of limited value in the evaluation of maxillary sinus disease. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019 March 2019;127(3):237-46. DOI: 10.1016/j.oooo.2018.10.005.

Constantine S, Keirmeier, A., Anderson, P. The Normal Fetal Cephalic Index in the Second and Third Trimesters of Pregnancy. Ultrasound quarterly. 2019;Publish Ahead of Print. DOI: 10.1097/ruq.0000000000000444.

Constantine S, Keirmeier, A., Anderson, P. The Prenatal Detection of Isolated Fetal Sagittal Craniosynostosis May Assist with Delivery Planning. Submitted for publication, 2019.

Poster Presentations

Constantine S, David D, Anderson P. The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis.

10th Annual Florey Postgraduate Research Conference, University of Adelaide, September 2016.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Results of the CACO study - Carotid Artery Calcification on OPG.

11th Annual Florey Postgraduate Research Conference, University of Adelaide, September 2017.

Constantine S, Keirmeier, A., Anderson, P. The Normal Fetal Cephalic Index.

Australian Society for Medical Research SA Scientific Meeting, June 2018.

Constantine S, Keirmeier, A., Anderson, P. The Normal Fetal Cephalic Index.

12th Annual Florey Postgraduate Research Conference, University of Adelaide, September 2018.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Carotid Artery Calcification on Orthopantomograms (CACO Study) - is it indicative of carotid stenosis?

International Association of Dental Research 58th Annual Scientific Meeting, Sep 2018.

Constantine S, Keirmeier, A., Anderson, P. The Antenatal Diagnosis of Isolated Sagittal Craniosynostosis.

Electronic Poster https://wfumb2019.paperlessevents.com.au/posters/#iframe

17th World Federation for Ultrasound in Medicine and Biology Congress, Sep 2019.

The Use of Obstetric Ultrasound in the Antenatal Diagnosis of Craniosynostosis.

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THE UNIVERSITY of ADELAIDE
SCHOOL OF DENTISTRY

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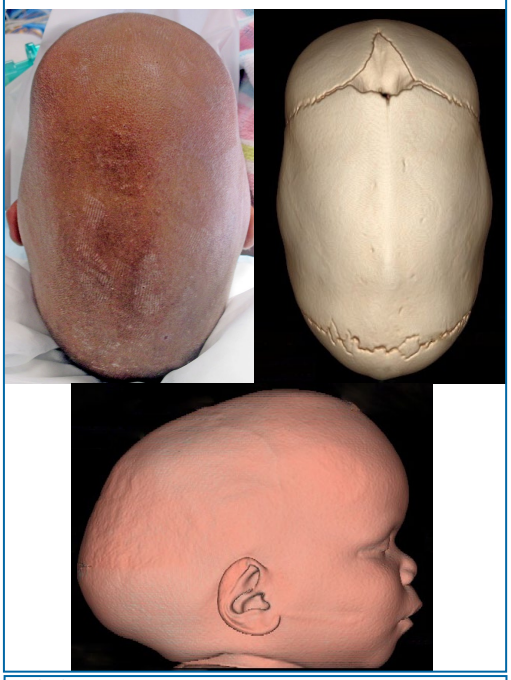
Introduction:

Craniosynostosis, or the premature fusion of the cranial sutures, occurs in approximately 1 in 2500 live births.[1] Most of these are isolated (non-syndromic) sutural fusions with 15% occurring as part of a craniofacial syndrome.[2] The cranial sutures allow for growth of the developing brain in both the pre- and post-natal period but also play a crucial role in vaginal delivery. The patent sutures allow moulding of the fetal skull to facilitate passage through the birth canal. There are only a handful of published reports that describe the delivery problems associated with craniosynostosis, in particular sagittal synostosis,[3–5] and the morbidity to both mother and child as a result.



Methods:

The antenatal imaging for patients presenting to the WCH with sagittal craniosynostosis born between 1 January 2000 and 31 December 2014 was traced. The fetal cranial measurements including biparietal diameter (BPD), occipitofrontal diameter (OFD) and head circumference (HC) were recorded. Measurements were recorded from the morphology scan (performed between 17 and 23 weeks) and a third trimester growth scan. The cephalic index (CI) was calculated for each affected fetus from measurements obtained at each scan using the formula (Jeanty et al.[6]):

$$CI = BPD/OFD \times 100$$

The CI was considered normal if between 75 and 85.[6,7] The method of delivery of each child was recorded, including the reason for any interventional deliveries. Where the information was available, pelvic injuries to the mother as a result of the delivery were also recorded. Data were compared to the state-wide data provided by the South Australian Pregnancy Outcome Unit[8].

Results:

There were 118 children born in SA/NT during the 15-year audit period who have been diagnosed with sagittal craniosynostosis. 75% of children have an isolated sagittal synostosis (see table below).

	Number of fetuses (%)	Isolated sagittal synostosis	Multiple synostoses	Recognised craniofacial syndrome
Male	82 (69)	60	12	7
Female	36 (31)	29	7	2
Total	118 (100)	89	19	9

Data from at least one obstetric scan were obtained for 89 of the 118 pregnancies (75%), and data from two scans were obtained for 28 patients (24%). Morphology scans were available for 82 pregnancies (69%) and growth scans in 37 pregnancies (31%). The majority of pregnancies did not have any formal ultrasound scans after 20 weeks. The CI was calculated from the morphology scan for 80 fetuses who developed sagittal synostosis (Figure 1).

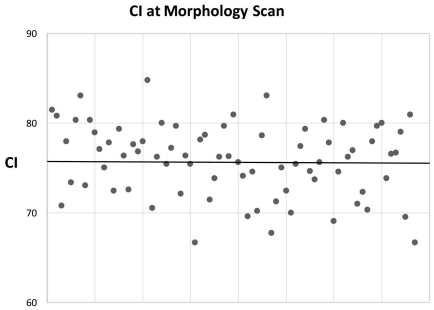


Figure 1: Distribution of the cephalic index (CI) of fetuses who developed sagittal synostosis. These measurements were obtained at the routine morphology scan performed between 17 and 22 weeks gestation. The mean CI was 76.

Twenty-six fetuses (33%) had a CI below the normal range. The mean CI was 76 (67–85), standard deviation (SD) = 4. The CI was calculated in the third trimester for 36 fetuses who developed sagittal synostosis (Figure 2).

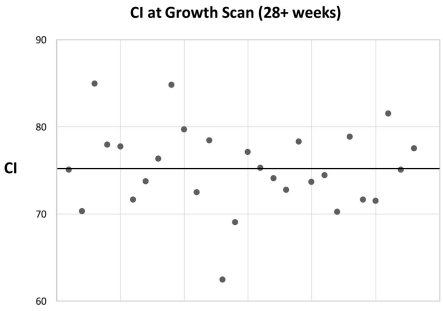


Figure 2: Distribution of the cephalic index (CI) of fetuses who developed sagittal synostosis. These measurements were obtained at third trimester growth scan performed after 26 weeks gestation. The gestation for each fetus varied, as the scans were performed for a variety of clinical indications. The mean CI was 75.

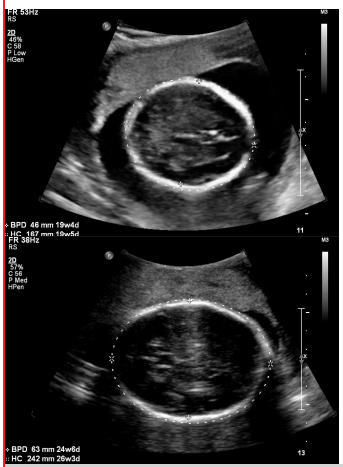
In the group of children with isolated sagittal synostosis the CI was below the normal range in 31% of available scans in the second trimester and in 54% of available scans in the third trimester. Twenty-one fetuses had scans available from both second and third trimesters. The CI reduced significantly between second and third trimesters in eight (33%) fetuses. The mean change in CI was -2 (range -13 to 9). A diagnosis of craniosynostosis was suspected antenatally in only 7 of the 168 cases with imaging available for review (4.8%). In a further five cases (3%), a comment was made about an unusual fetal head shape in the ultrasound report, but this was dismissed or not followed up. On retrospective review of the available antenatal imaging, the diagnosis of sagittal synostosis is strongly suggested in several cases. A progressive reduction in CI indicating progressive scaphocephaly in late pregnancy has been demonstrated in a number of cases. In all these cases, the CI in the late third trimester was below 75.

The mode of delivery was also recorded. A total of 112 pregnancies were included. The data were compared with the total population data in SA over the same time period[8] (see table below). There was an increase in the number of emergency caesarean deliveries in women whose fetuses had sagittal synostosis when compared with the general population (21% vs. 17%). There were also a higher number of emergency caesarean sections performed for CPD and failure to progress in the study group compared with the general population. There were 15 fetuses who had a CI of under 75 at the third trimester scan.

	Sagittal synostosis (%)	SA population (%)
Emergency section	22	17
Failure to progress, CPD	61	50

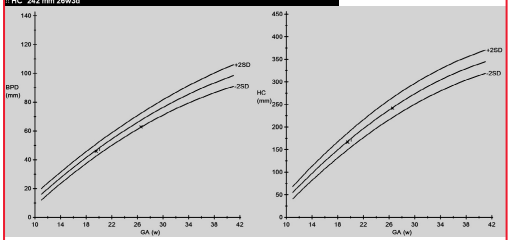
Case 1.

Thirty-year-old woman: The morphology scan showed a normal fetus with both BPD and HC on the mean and a CI of 81. A growth scan at 26+ weeks showed the HC to being growing along the mean, but the BPD now on the 5th percentile. The head shape is clearly more scaphocephalic and the CI has reduced to 74. The child was delivered by emergency caesarean section due to breech presentation in labour.



Axial cranial image and measurements at the morphology scan.

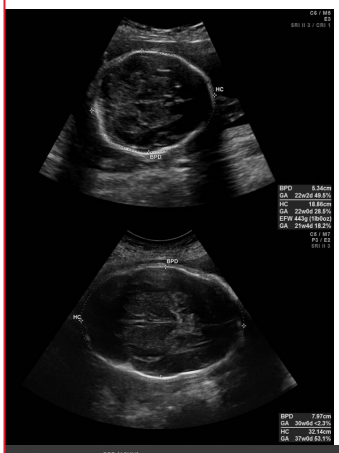
Axial cranial image and measurements at 27 weeks.



Graphic representation of the biparietal diameter (BPD) and head circumference (HC) measurements, showing appropriate head growth along the 50th percentile. The axial images show the fetal head becoming more dolichocephalic as the pregnancy progressed. This is confirmed by the stable growth of the HC, but dropping growth of the BPD.

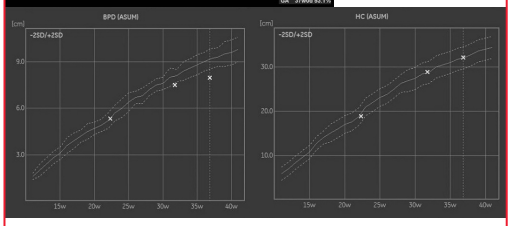
Case 2.

Thirty-six-year-old woman: The morphology scan showed a normal 22-week fetus with a BPD and HC close to the mean. The CI was calculated at 78. A growth scan at 32 and again at 37 weeks shows progressive scaphocephaly, with the HC remaining on the mean and the BPD dropping below the 5th percentile. The CI at 37 weeks had reduced to 68. The child was delivered by emergency caesarean section for fetal distress due to prolonged labour without progression.



Axial cranial image and measurements at the morphology scan.

Axial cranial image and measurements at 37 weeks.



Graphic representation of the biparietal diameter (BPD) and head circumference (HC) measurements, showing appropriate head growth along the 50th percentile. The axial images show the fetal head becoming more dolichocephalic as the pregnancy progressed. This is confirmed by the stable growth of the HC, but progressive drop in growth of the BPD.

Discussion:

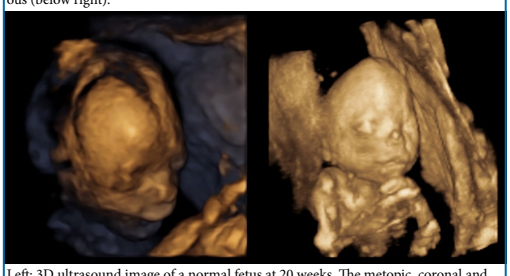
The causes and timing of onset of craniosynostosis is still not clear. There have been suggestions made that fetal constraint may play a role in some cases,[5,9] and a number of genes have been identified as being involved. The cause is almost certainly multifactorial. The time of onset is also likely to be variable, which may explain our observation of a very large change in CI in some affected fetuses, and very little change in others.

Our data suggest that a CI below the normal range, especially in the third trimester, should prompt careful evaluation of the cranial sutures, and consideration should be given to a further antenatal scanning late in the third trimester to re-examine the fetal skull and CI.

Cephalopelvic disproportion can be difficult to diagnose clinically by even the most experienced obstetrician.[10] Half of the emergency sections performed in SA are because of CPD, with a further 12% due to malpresentation[8]. Higher rates of malpresentation, including breech presentation, have been reported in fetuses later diagnosed with craniosynostosis.[3]

To our knowledge, the observation of a serial reduction in CI during pregnancy as detected by ultrasound scanning has not previously been reported. While this was not a feature seen in every case of sagittal synostosis, our cases resulted in emergency caesarean deliveries for malpresentation and/or obstructed labour. Recognition of this feature antenatally could prevent this situation by planning an elective caesarean section.

We have also been able to identify the cranial sutures with three-dimensional (3D) ultrasound in the second and early third trimester. The open sutures and anterior fontanelle are clearly seen in this normal fetus (below left), while in this 20- week fetus subsequently diagnosed with Pfeiffer syndrome, global craniosynostosis is obvious (below right).



Left: 3D ultrasound image of a normal fetus at 20 weeks. The metopic, coronal and anterior sagittal sutures are clearly patent and well-demonstrated.

Right: 3D ultrasound image in a 20-week fetus later diagnosed with Pfeiffer syndrome. The metopic and coronal sutures are fused in keeping with global craniosynostosis. This was confirmed at autopsy.

Conclusion:

Our data suggests that craniosynostosis could be diagnosed antenatally in a significant number of cases. The routine calculation of CI can be performed at antenatal scanning, and a value outside the normal range, or a change in CI during the pregnancy should prompt detailed scanning of the fetal skull and cranial sutures, including 3D scanning. An increase in antenatal diagnosis will enable better delivery planning for this group of patients, which should lead to a decrease in fetal and maternal morbidity as a result of obstructed labour.

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Women's and Children's Hospital
ADELAIDE

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Dr Denise Roach[1,2]
Assoc Prof Sharon Liberali[1,3]
Dr Andreas Kiermeier[4]
Dr Paroma Sarkar[2]
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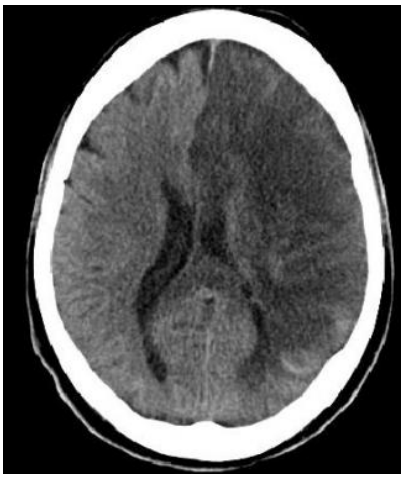
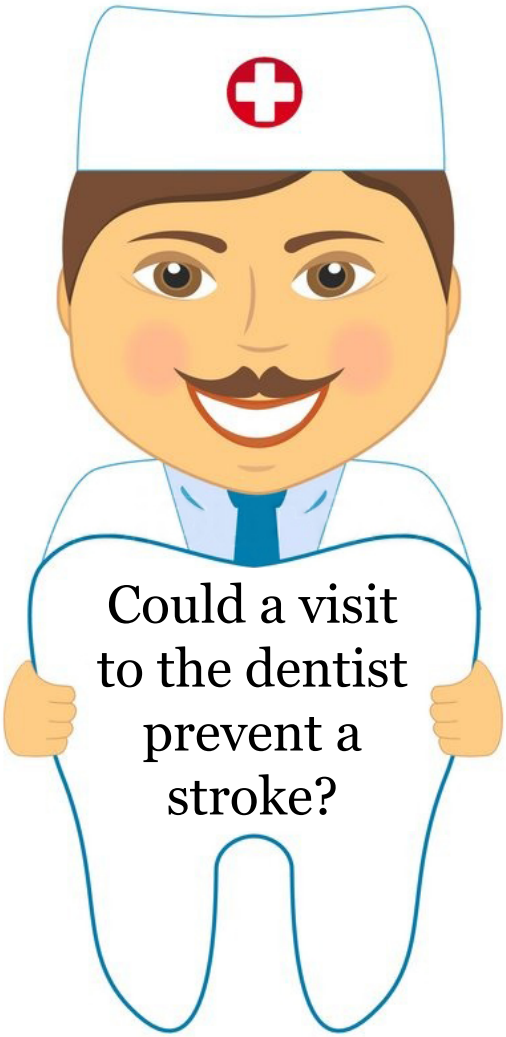
5. Royal Adelaide Hospital
6. Women's and Children's Hospital

Results of the CACO study (Carotid Artery Calcification on OPG).

Stroke is one of Australia's biggest killers and a leading cause of disability.[1]

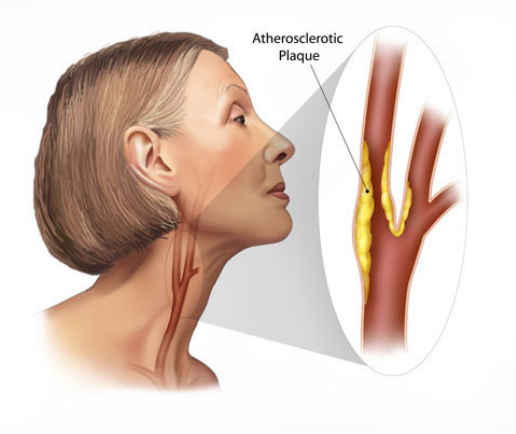
1 in 6 people will have a stroke.[2]

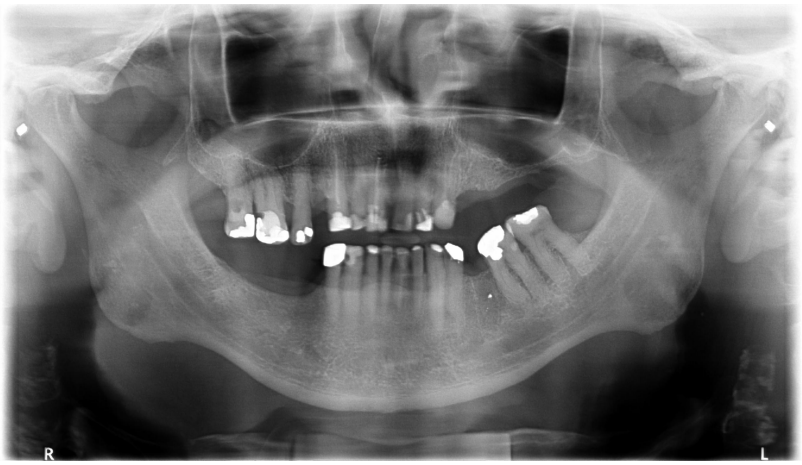


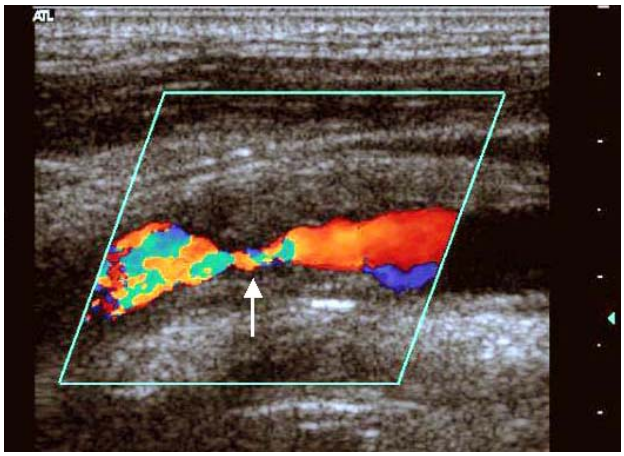


The financial cost of stroke in Australia is estimated to be $5 billion per year.[3]

More than 80% of stokes can be prevented.[4]







- 5 780 dental OPGS
- 10.8% carotid artery calcification
- 233 carotid ultrasound examinations
- 233 patient vascular risk histories

- 11.2% carotid artery stenosis ≥50%
- 77% with carotid artery calcification

- Hypertension was a significant predictor of carotid stenosis (OR 5.0, p=0.03)
- CAC had an OR of 2.4 for detecting carotid artery stenosis (p=0.11)

- Carotid calcification should provoke a review of the patient's vascular risk factors

1. Australian Institute of Health and Welfare 2016. Australia's Health 2016.
2. Seshadri S., Wolf P.A. (2007). "Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study." The Lancet Neurology 6(12), 1106-14.
3. Deloitte Access Economics - The economic impact of stroke in Australia, 2013.
4. O'Donnell,et al , Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study Lancet 2016; 388: 761–75.

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adelaide.edu.au

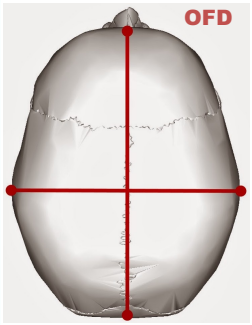
The Normal Fetal Cephalic Index.

Sarah Constantine[1,2], Peter Anderson[1,3], Andreas Kiermeier[4].

[1] University of Adelaide, School of Dentistry. [2] Women's and Children's Hospital, Department of Medical Imaging.
[3] Australian Craniofacial Unit. [4] Statistical Process Improvement Consulting and Training Pty Ltd.

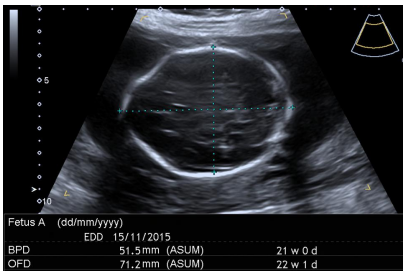
BACKGROUND:

The cephalic index (CI) is the ratio of the biparietal diameter (BPD) to the occipitofrontal diameter (OFD) of the skull. It is routinely used in craniofacial surgery to evaluate skull shape.



CI = BPD/OFD x 100

The normal CI in early childhood is 76 to 81[1], but there has been little research into the normal CI prior to birth.



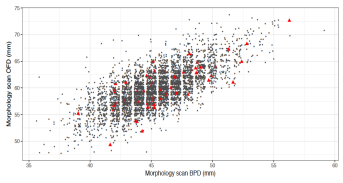
The CI can be calculated during routine pregnancy ultrasound scans.

METHODS:

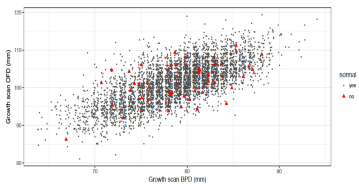
Data was obtained from 4 304 pregnancies. Scans were performed at 17 – 22 weeks gestation and at 28 – 33 weeks gestation. The BPD and OFD were measured, and the CI was calculated at each scan.

RESULTS:

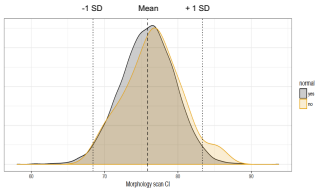
The CI measured in both the second and third trimesters was very close to a Normal distribution (Figure). The mean CI at 17 – 22 weeks was 75.9 (SD 3.7) and the mean CI at 28 – 33 weeks was 77.8 (SD 3.5).



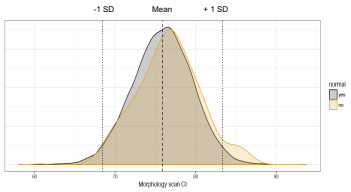
Scatter plot of OFD vs BPD at 17 – 22 weeks gestation.



Scatter plot of OFD vs BPD at 28 – 33 weeks gestation.



Density plot of CI at 17 – 22 weeks gestation.

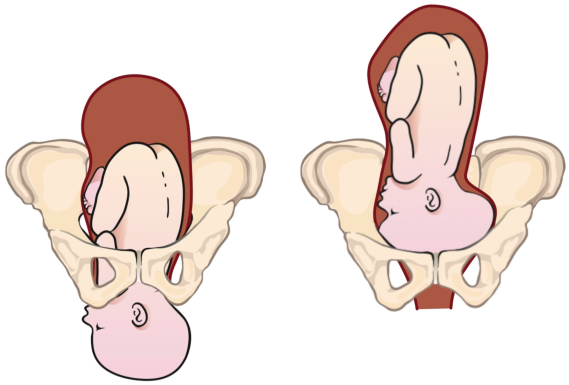


Density plot of CI at 28 – 33 weeks gestation.

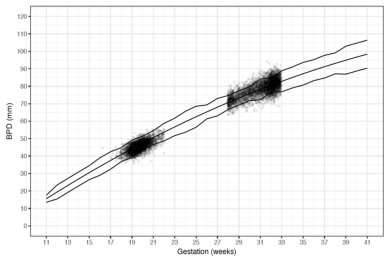
CONCLUSIONS:

1. The normal range for the fetal cephalic index has been established.
2. There is great variation in the CI throughout pregnancy, and the head shape of an individual fetus can change during pregnancy.
3. This means isolated measurements of the fetal cephalic index are of minimal value in detecting an abnormal skull shape.

The shape of the fetal head may impact upon delivery. The cranial sutures allow the head to mould as it passes through the mother's pelvis. If the head is abnormally shaped, labour may become obstructed[2].

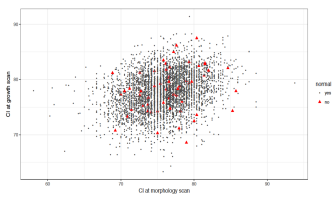


The fetal measurements correlated well with the established population curves[3], indicating the study group was representative of the normal population.

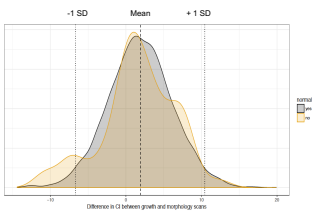


Scatter plot of BPD vs gestational age, including ASUM population standards.

There was wide variation in the CI values at both scans, with limited association between values at both scans. The mean CI was slightly higher in later pregnancy with an average increase of 1.9 (SD 4.28) but this was not significant (t = 0.656, p = 0.512, 95% confidence). There was no association with fetal presentation at delivery.



Scatter plot of CI at 17 – 22 weeks vs 28 – 33 weeks gestation.



Density plot of the change in CI during pregnancy.

REFERENCES:

1. Likus W et al. Cephalic Index in the First Three Years of Life: Study of Children with Normal Brain Development Based on Computed Tomography. Scientific World Journal 2014; http://dx.doi.org/10.1155/2014/502836.
2. Anderson PJ, McLean NR, David DJ. Craniosynostosis and childbirth. European Journal of Plastic Surgery 2005; 28(2): 94 – 8.
3. Australasian Society for Ultrasound in Medicine. Guidelines, Policies and Statements D7: Statement on Normal Fetal Measurements. Sydney: ASUM; 2001.

The Normal Fetal Cephalic Index.

THE UNIVERSITY of ADELAIDE

Sarah Constantine[1,2], Andreas Kiermeier[3], Peter Anderson[1,4].

[1] University of Adelaide, School of Dentistry.
[2] Women's and Children's Hospital, Department of Medical Imaging.
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BACKGROUND:

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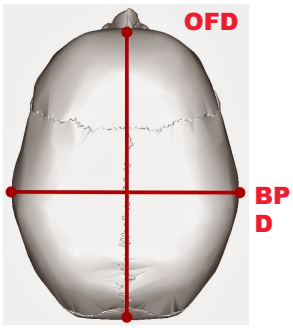

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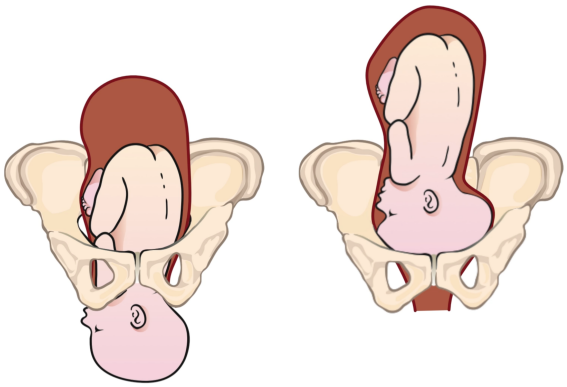
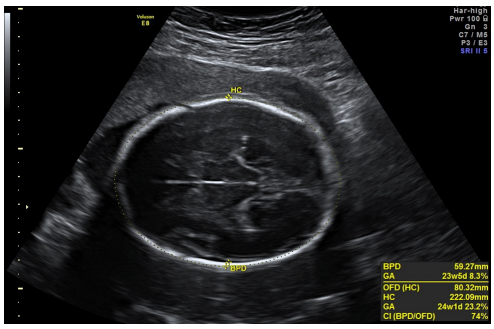


Diagram demonstrating how an abnormally narrow skull (right)can cause obstructed labour.

The shape of the fetal head may impact upon delivery. The cranial sutures allow the head to mould as it passes through the mother's pelvis. If the head is abnormally shaped, labour may become obstructed[2].



Routine pregnancy ultrasound showing the normal fetal cranial measurements, including the cephalic index.

The CI can be calculated during routine pregnancy ultrasound scans.

METHODS:

Data was obtained from 4 304 pregnancies. Scans were performed at 17 – 22 weeks gestation and at 28 – 33 weeks gestation. The BPD and OFD were measured, and the CI was calculated at each scan.

REFERENCES:

1. Likus W et al. Cephalic Index in the First Three Years of Life: Study of Children with Normal Brain Development Based on Computed Tomography. Scientific World Journal 2014; http://dx.doi.org/10.1155/2014/502836.
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RESULTS:

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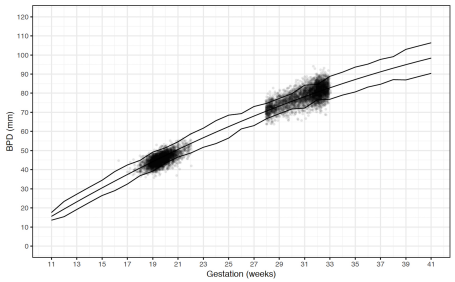
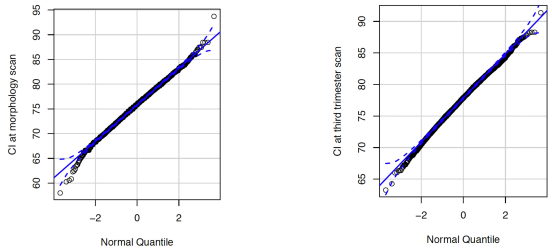


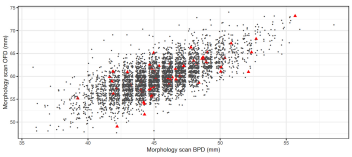
Scatter plot of BPD vs gestational age, including ASUM population standards.

The CI measured in both the second and third trimesters were very close to a Normal distribution.

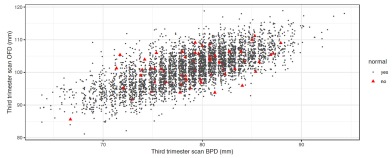


Normal quantile plots of the cephalic index showing the distribution is very close to a Normal distribution.

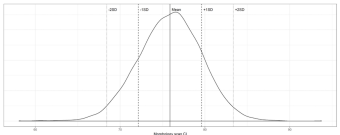
The mean CI at 17 – 22 weeks was **75.9** (SD 3.7) and the mean CI at 28 – 33 weeks was **77.8** (SD 3.5).



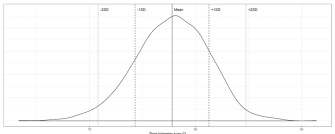
Scatter plot of OFD vs BPD at 17 – 22 weeks gestation.



Scatter plot of OFD vs BPD at 28 – 33 weeks gestation.



Density plot of CI at 17 – 22 weeks gestation.



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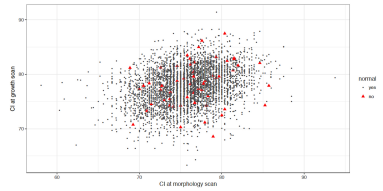

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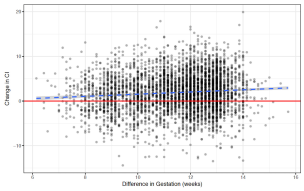


Scatter plot of the change in cephalic index between growth and morphology scans versus the corresponding change in gestation age.

CONCLUSIONS:

1. The normal range for the fetal cephalic index has been established.
2. There is variation in the CI throughout pregnancy, and the head shape of an individual fetus can change during pregnancy.
3. The fetal population tended to become more brachycephalic as pregnancy progresses.
4. Isolated measurements of the fetal cephalic index are of minimal value in detecting an abnormal skull shape.

Carotid Artery Calcification on Orthopantomograms

Is it indicative of carotid artery stenosis? The CACO Study.

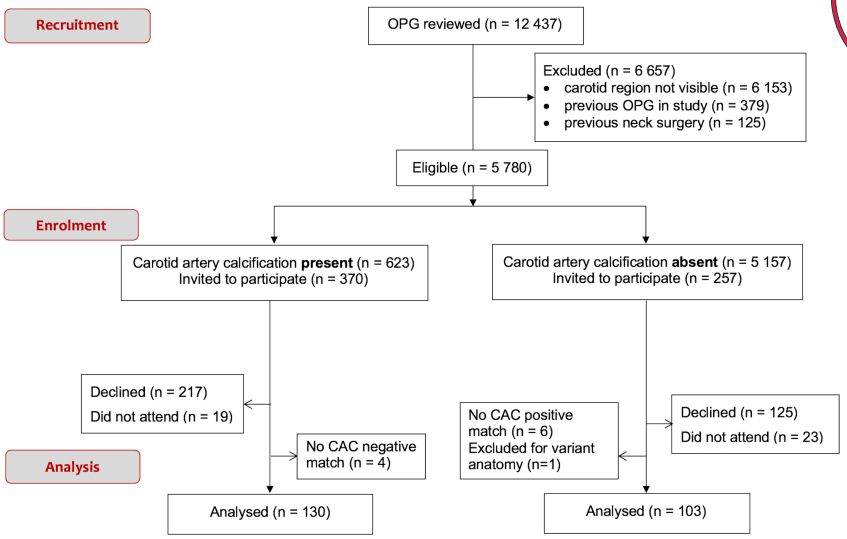
Dr Sarah Constantine FRANZCR
Dr Denise Roach FRACS(Vasc Surg)
Associate Professor Sharon Liberali FRACDS(SND)
Dr Andreas Kiermeier PhD(Stat)
Dr Paroma Sarkar MBBS
Associate Professor Jim Jannes FRACP
Dr Paul Sambrook FRACDS(OMS)
Professor Peter Anderson FRACS
Professor John Beltrame FRACP

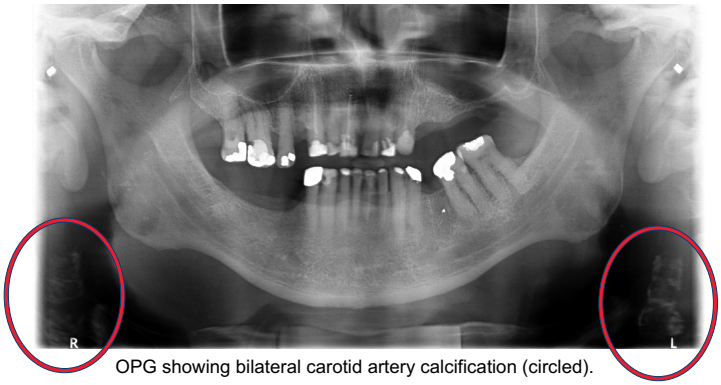
Background.

It is unclear whether incidental carotid artery calcification (CAC) on radiographs has a defined relationship to clinically significant carotid artery stenosis, and therefore risk of stroke. The primary objective of this study was to ascertain the relationship between dental radiograph detected carotid calcification and carotid artery stenoses ≥ 50% on carotid duplex ultrasound.

Methods.

An observational study of patients undergoing routine dental orthopantomogram (OPG) examinations. Consecutive patients with CAC on OPG were prospectively matched to those without CAC based on age and gender. Ultrasound of the carotid arteries was performed to determine the presence of stenosis (≥ 50%) in either vessel.





OPG showing bilateral carotid artery calcification (circled).

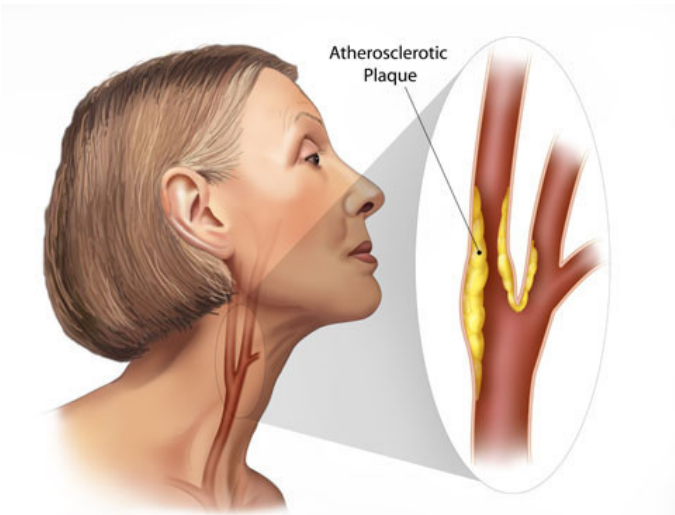
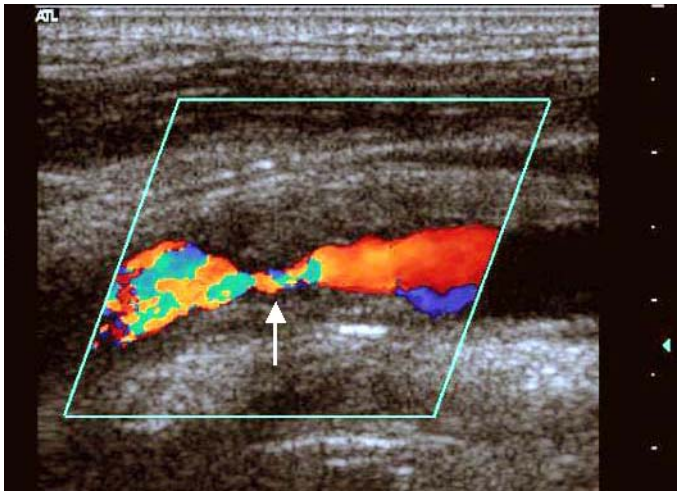


Diagram showing the location of the carotid artery in the neck, and where the narrowing occurs.

Results.

- Of 5,780 consecutive OPG examinations with suitable images for analysis, CAC was detected in 10.8%.
- A total of 233 patients underwent carotid ultrasound (130 with CAC and 103 without CAC on OPG).
- The prevalence of a clinically significant (≥ 50%) carotid stenosis on ultrasound was 15.4% (20/130) in those with CAC and 5.8% (6/103) for those without CAC on OPG.
- The sensitivity and specificity of carotid artery calcification on OPG for identifying significant carotid artery stenosis were 77% and 47% respectively.
- The positive and negative predictive values of carotid artery calcification on OPG for predicting carotid artery narrowing were 15% and 94% respectively.



Colour Doppler ultrasound of a carotid artery showing a tight stenosis

Conclusions.

- Incidental CAC detected on routine OPG requires both radiological reporting and clinical follow-up since 1 in 7 patients will have a clinically significant carotid artery stenosis as compared with 1 in 20 patients who do not have CAC.
- OPG is not suitable as a screening test for carotid artery stenosis due to the low sensitivity and specificity.
- As 1 in 6 people will suffer a stroke[1], and the financial cost of stroke in Australia is estimated at $5 billion per year[2], further study is needed into the cost-benefit of performing routine ultrasound on this asymptomatic population.

References.

1. Sheshadri S, Wolf PA. (2007) Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. The Lancet Neurology 6(12), 1106-14.
2. Deloitte Access Economics – The economic impact of stroke in Australia, 2013.

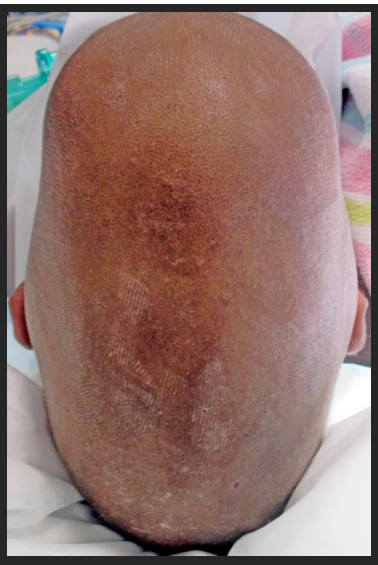
Trial Registration: Australian and New Zealand Clinical Trials Registry Website (U1111-1148-1066).
http://www.ANZCTR.org.au/ACTRN12613001038785.aspx

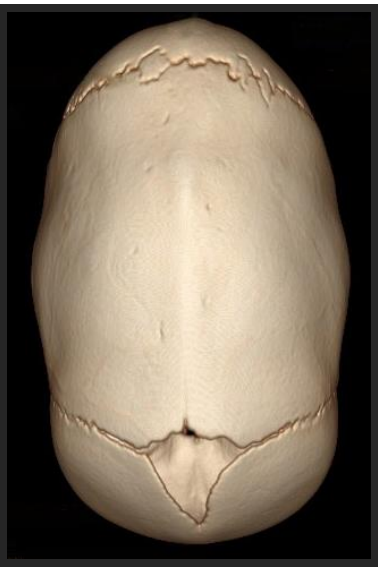
The Antenatal Diagnosis of Isolated Sagittal Craniosynostosis.

Dr Sarah Constantine MBBS, FRANZCR.
Perinatal Radiologist, Women's and Children's Hospital,

Dr Andreas Kiermeier PhD(Stat).
Director, Statistical Process Improvement Consulting and Training Pty Ltd, SA.

Professor Peter Anderson DSc, DDSc, MD(Edin), PhD, MSurg(Melb), MFST(Ed), FDSRCS(Ed), FDSRCS (Eng), FRCS(Eng), FRCS(Plast.), FACS, FRACS.
Director of Research, Australian Craniofacial Unit, Women's and Children's Hospital, SA.





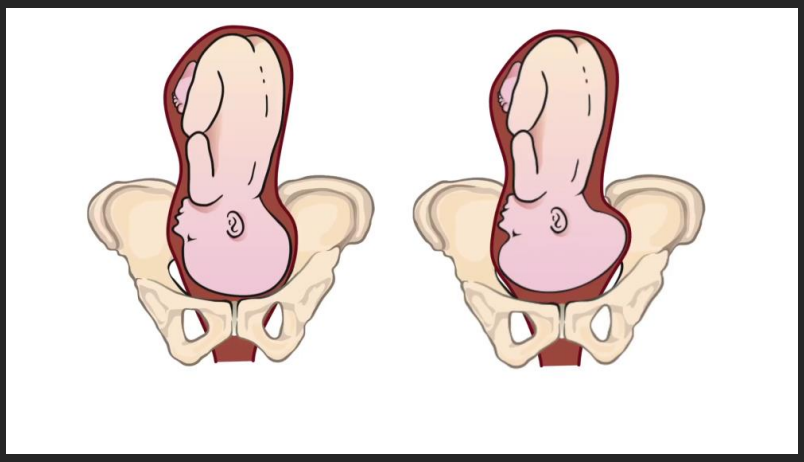
Photograph and CT scan of an infant with isolated sagittal synostosis. Note the scaphocephalic head shape and fused midline suture. The remaining cranial sutures are patent.

Introduction

- Isolated sagittal craniosynostosis is rarely diagnosed antenatally, but is often associated with obstructed labour.

- The study investigated fetal ultrasound markers of sagittal synostosis.

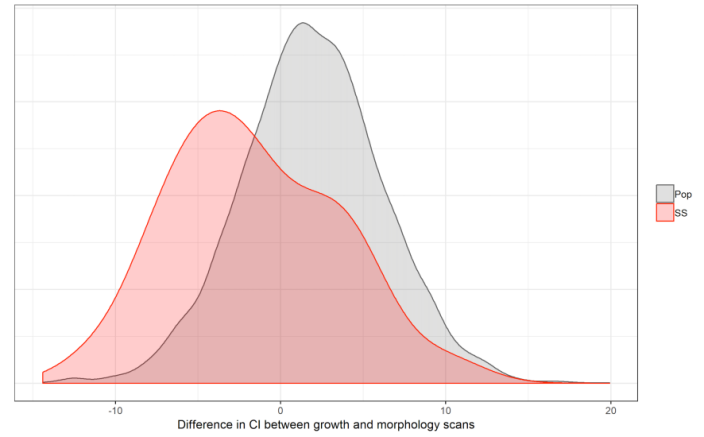
Normal infant Scaphocephalic infant



Animation showing why sagittal synostosis can cause obstructed labour. The fused suture causes scaphocephaly that prevent head moulding during delivery.

Methods.

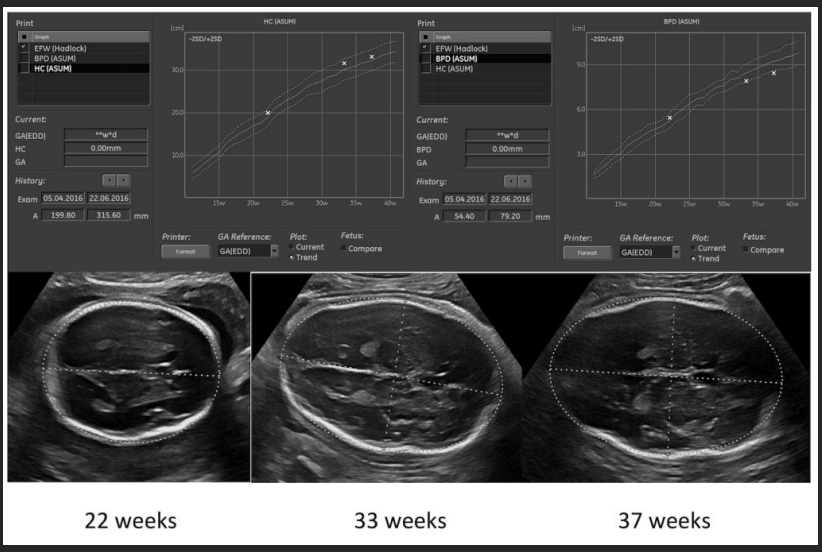
- Antenatal ultrasound scans of children diagnosed with sagittal synostosis were compared to those of normal infants.



Difference in the change in cephalic index (CI) between the normal population (Pop) and the infants with sagittal synostosis (SS). The mean CI increases slightly for the normal population, but decreases in infants with isolated sagittal synostosis.

Results.

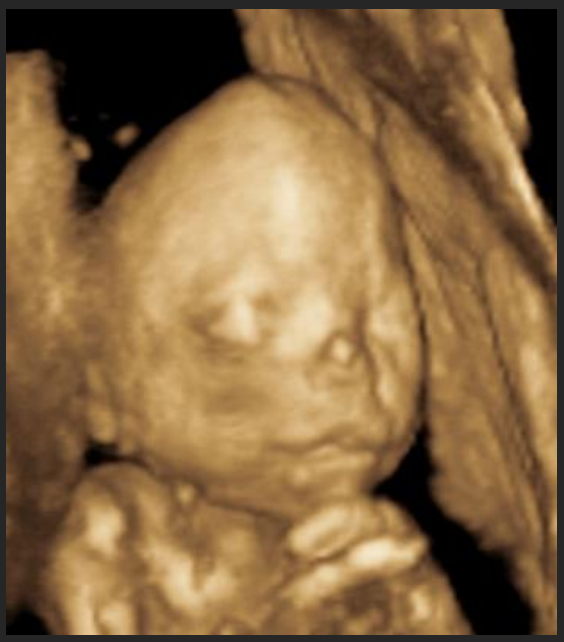
- Affected infants tended to show progressive scaphocephaly in the third trimester.
- Normal infants showed minimal change in cranial shape but tended towards brachycephaly.



Example of progressive scaphocephaly in an infant diagnosed with isolated sagittal synostosis post-natally. Note the flattening of BPD growth curve.

Results.

- The head circumference of affected infants grows parallel to the mean, but the biparietal diameter growth flattens progressively.



Example of 3D ultrasound showing fusion of the midline sutures in the fetus.

Conclusions.

- Isolated sagittal synostosis is rarely detectable at the 20 week morphology scan, but can be diagnosed in the third trimester by a progressive reduction in the fetal cephalic index.

- A progressive reduction in cephalic index throughout the third trimester should provoke 3D imaging to better examine the sagittal suture.

Oral Presentations

Constantine S, David D, Anderson P. The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better.

Royal Australian and New Zealand College of Radiologists 66th ASM, October 2015.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. The Significance of the Presence of Carotid Artery Calcification on OPG.

Royal Australian and New Zealand College of Radiologists 66th ASM, October 2015.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Carotid Artery Calcification on Orthopantomograms (CACO Study) - is it indicative of carotid stenosis?

Adelaide Dental School Research Day, August 2018.

Prizes/Awards

Constantine S, David D, Anderson P. The use of obstetric ultrasound in the antenatal diagnosis of craniosynostosis: We need to do better. Australasian Journal of Ultrasound in Medicine. 2016;19(3):91-8. DOI: 10.1002/ajum.12016.

Australasian Society of Ultrasound in Medicine AJUM Article of the Year Award 2017.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Carotid Artery Calcification on Orthopantomograms (CACO Study) - is it indicative of carotid stenosis?

Adelaide Dental School Research Day, August 2018. Best PhD/MPhil Student Presentation in Dentistry.

Constantine S, Roach D, Liberali S, Kiermeier A, Sarkar P, Jannes J, Sambrook, P, Anderson, P, Beltrame, J. Carotid Artery Calcification on Orthopantomograms (CACO Study) - is it indicative of carotid stenosis?

Adelaide Dental School Research Day, August 2018. Colgate Competition Winner.

ASUM
Promoting Ultrasound Excellence

The Australasian Society for Ultrasound in Medicine

awards

Sarah Constantine

AJUM Article of the Year

Dated this 7th day of October 2017

George Condous
President

Lyndal Macpherson
Chief Executive Officer

THE UNIVERSITY of ADELAIDE

This is to certify that

Dr Sarah Constantine

was awarded

Best PhD/MPhil Student Presentation in Dentistry

for Outstanding Academic Achievement at the
2018 Adelaide Dental School Research Day

[redacted]

Professor Richard Logan

10 August, 2018

Date

Sub Cruce Lumen

Colgate

THE UNIVERSITY of ADELAIDE

This is to certify that

Dr Sarah Constantine

was awarded

Colgate Competition Winner

for Outstanding Academic Achievement at the
2018 Adelaide Dental School Research Day

Professor Richard Logan

10 August, 2018

Date

Colgate

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