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Nuchal translucency as a method of first trimester screening for aneuploidy in a South African population

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynecology

DECLARATION

I, Dr Poovangela Naidoo declare that this thesis is my own work. It is being submitted for the degree of Masters of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr P Naidoo

On this 27th day of September,2006.

DEDICATION

In loving memory
Of my brother
Suri Naidoo
1968-1988

PUBLICATIONS AND PRESENTATIONS

Two presentations emanated from this study:

1. 25 June 2005 - Interdepartmental research day.
2. 11 May 2006 – Pretoria Update, International Convention Center, Pretoria.

ABSTRACT

Nuchal Translucency as a method of First Trimester Screening for Aneuploidy in a South African population

Background
Chromosomal abnormalities constitute 15% of congenital abnormalities and 50% of pregnancy losses. Twenty-five percent of these will be Trisomy 21. Down's syndrome has a birth incidence of 2 per 1000 and constitutes 25% of severe mental handicap in the developed world. Whereas the risk assessment focuses on Trisomy 21, the fetuses that screen positive are also known to contain other defects, which include anomalies such as cardiac defects, diaphragmatic hernias, neuromuscular disorders, and rare genetic syndromes.

Objective
To determine the effectiveness of nuchal translucency (NT) screening in predicting aneuploidy and structural abnormalities in a South African population

Setting
Chris Hani Baragwanath Hospital Fetal Medicine Unit

Study design
Descriptive Study

Methodology
The Fetal Medicine Unit database was reviewed and the records of patients who had undergone NT screening between July 2003 and July 2005 were retrieved. There were no exclusions. An adjusted risk was derived from the combination of age-related risk and the risk derived from nuchal translucency screening. A positive screen was denoted by an adjusted risk of more than 1/300 and a negative screen was denoted by an adjusted risk of less than 1/300.

Results
A total of 428 patients had first trimester screening during this period. Thirteen patients (3%) were lost to follow up. Of the 415 cases that were analyzed, 57 patients screened positive and 356 patients screened negative. In addition, 2 fetuses with acrania were detected. The mean age for both groups of patients was 30.1 years. The crown-rump length of fetuses with a positive screen was statistically significantly shorter than fetuses that screened negative. Of the 57 patients that screened positive 24 elected to have chorionic villus sampling (CVS) which resulted in the detection of 6 chromosomal abnormalities and 2 structural abnormalities. Of the remaining 356 patients, who had screened negative, 2 had an increased adjusted risk, and one chromosomal abnormality was detected in this group.
Of the remaining 354 patients, 8 elected to have CVS because of a previous history of chromosomal abnormality. All of them proved to be normal.

Conclusions
The use of such screening has enabled prenatal karyotyping to be focused on pregnancies at highest risk for chromosomal abnormalities regardless of age.

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TABLE OF CONTENTS Page

DECLARATION....ii
DEDICATION....iii
PUBLICATIONS AND PRESENTATIONS....iv
ABSTRACT....v
ACKNOWLEDGMENTS....vi
TABLE OF CONTENTS....vii
TABLE OF FIGURES....ix
LIST OF TABLES....x

1. INTRODUCTION....1
1.1 BACKGROUND....1
1.1.1 THE BURDEN OF CONGENITAL DISORDERS....1
1.1.2 CALCULATION OF RISK FOR CHROMOSOMAL DISORDER....3
1.1.2.1 MATERNAL AGE AND GESTATIONAL AGE....4
1.1.2.2 PREVIOUS CHROMOSOMAL ABNORMALITIES....6
1.1.3 NUCHAL TRANSLUCENCY....7
1.1.3.1 HISTORICAL ASPECTS....7
1.1.3.2 NUCHAL TRANSLUCENCY OR CYSTIC HYGROMA?....8
1.1.3.3 FETAL NUCHAL FLUID- PHYSIOLOGICAL OR PATHOLOGICAL? 9
1.1.3.4 THE FETAL MEDICINE FOUNDATION PROJECT - NUCHAL TRANSLUCENCY AND ANEUPLOID FETUSES....9
1.1.3.5 NUCHAL TRANSLUCENCY AND EUPLOID FETUSES....11
1.1.3.6 THE OPTIMAL GESTATIONAL AGE TO EXAMINE FETAL NUCHAL TRANSLUCENCY....13
1.1.4 SCREENING THE GENERAL POPULATION....13
1.1.5 THE ANATOMICAL SURVEY....14
1.1.6 BIOCHEMISTRY AND SEQUENTIAL SCREENING....15
1.1.7 DIAGNOSIS BY INVASIVE TESTING....15
1.1.7.1 MATERNAL ACCEPTANCE OF CHORIONIC VILLUS SAMPLING.16
1.1.8 IMPROVING THE SENSITIVITY OF FIRST TRIMESTER SCREENING.16
1.1.8.1 SONOGRAPHIC ASSESSMENT OF DUCTUS VENOSUS FLOW....16
1.1.8.2 SONOGRAPHIC ASSESSMENT OF THE NASAL BONE....17
1.1.9 MULTIPLE PREGNANCIES....19
1.1.9.1 TYPES OF MULTIPLE PREGNANCIES....19
1.1.9.2 SCREENING FOR ANEUPLOIDY IN TWIN PREGNANCIES....19
1.2 PURPOSE OF THE STUDY....21
1.3 SETTING....21
1.4 OBJECTIVES....24
1.5 STUDY DESIGN....24
2. MATERIALS AND METHODS....25
2.1 STUDY SAMPLE-Study population, timing and sampling....25
2.2 DATA COLLECTION....25

2.3 THE MEASUREMENT OF NUCHAL TRANSLUCENCY 26
2.3.1 EQUIPMENT 26
2.3.2 INTER-OBSERVER VARIABILITY 27
2.3.3 SONOGRAPHIC CRITERIA TO MAXIMIZE QUALITY OF NUCHAL TRANSLUCENCY SCREENING 27
2.4 CALCULATION OF RISK 29
2.5 EVALUATION OF THE COST OF SCREENING 29
2.6 ANALYSIS OF RESULTS 29
3. RESULTS 31
3.1 FIRST TRIMESTER SCREENING OUTCOMES 31
3.2 FIRST TRIMESTER SCREENING CHARACTERISTICS 31
3.3 CHORIONIC VILLUS SAMPLING 32
3.3.1 GENDER DISTRIBUTION DERIVED FROM FETAL KARYOTYPE RESULTS 34
3.4 STRUCTURAL ABNORMALITIES DETECTED 34
3.5 TWIN PREGNANCIES 35
3.6 EVALUATION OF THE FIRST TRIMESTER SCREENING PROGRAMME 36
3.7 EVALUATION OF COST EFFECTIVENESS 36
4. DISCUSSION AND CONCLUSIONS 38
4.1 SCREENING CHARACTERISTICS 38
4.1.1 MATERNAL AGE 38
4.1.2 GESTATIONAL AGE 38
4.1.3 NUCHAL TRANSLUCENCY AND CROWN RUMP LENGTH 39
4.2 CHORIONIC VILLUS SAMPLING 39
4.2.1 INVASIVE PROCEDURE LOSS RATE 41
4.2.2 GENDER DISTRIBUTION 41
4.3 STRUCTURAL ABNORMALITIES DETECTED 41
4.4 FIRST TRIMESTER SCREENING IN TWIN PREGNANCIES 42
4.5 EVALUATION OF FIRST TRIMESTER SCREENING PROGRAM 43
4.6 COST EFFECTIVENESS OF THE CHRIS HANI BARAGWANATH HOSPITAL FIRST TRIMESTER SCREENING PROGRAM 44
4.7 CONCLUSION 45

ILLUSTRATION CREDITS 47
REFERENCES 48
APPENDIX A 54
APPENDIX B 55

LIST OF FIGURES

Figure **Page**

1-1 Maternal age-related risk for chromosomal abnormalities.....5
1-2 Gestational age-related risk for chromosomal abnormalities.....5
1-3 Ultrasound picture of a 12 week fetus with Trisomy 21….....8
1-4 Ductus venosus flow velocity waveform in a normal 13 week fetus……..……17
1-5 Nasal bone in a chromosomally normal fetus at 12 weeks…….……18
1-6 Absent nasal bone in a Trisomy 21 fetus at 12 weeks.....18
2-1 Midsagittal section of fetus at appropriate magnification.....28
2-2 Correct positioning of calipers.....28

LIST OF TABLES

Page

Table

1.1 Birth prevalence and outcomes of birth defects in populations of North European Origin.....2

1.2 Prevalence of Trisomy 21 by maternal age and gestational age.....6

1.3 Number of pregnancies with nuchal translucency above the 95th centile and the estimated risk for Trisomy 21 of 1:300 or greater.....10

1.4 Fetal abnormalities and genetic syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks gestation according to nuchal translucency thickness.....12

1.5 Criteria necessary for adequate visualization of fetal organs….....14

2.1 National health reference price list…….....29

3.1 First trimester screening characteristics…….....32

3.2 Summary of findings of chorionic villus sampling….....32

3.3 Gender distributions derived from karyotype results….....34

3.4 Structural abnormalities detected….....35

3.5 Results of first trimester screening in twin pregnancies.....35

3.6 Evaluation of the first trimester screening programme.....36

3.7 Cost effectiveness of the Chris Hani Baragwanath Hospital screening Programme.....37

1. INTRODUCTION

1.1 BACKGROUND

The use of first trimester screening to detect chromosomal and structural abnormalities is well established.[1,2,3] The first trimester screening programme which incorporates maternal age derived background risk, nuchal translucency measurement, the presence of a nasal bone, and biochemical screening, was designed by the Fetal Medicine Foundation in London. It is used in many institutions in South Africa. However, data on its use in a predominantly black South African population is limited.

The ethnic diversity of the South African population, as well as the financial constraints, limits the scope of health practice. Health care costs have risen above inflation over the last decade, with only marginal increments in the health budget, and as a result many first trimester screening centers in Gauteng have been forced to omit biochemical screening.

This study is an attempt to evaluate the use of a first trimester screening programme, without biochemical screening, in a predominantly black population.

1.1.1 THE BURDEN OF CONGENITAL DISORDERS

For the purpose of this study the definition of a congenital abnormality, will be that employed by Christianson, *et al*[4], which refers to conditions of prenatal origin, with structural defects, functional abnormalities, inborn errors of metabolism and chromosomal aberrations.

Congenital anomalies in rural black South African neonates occur in 15.23 per 1000 live births[5]. It has been estimated that the cumulative incidence by age 5 years of serious genetic disorders and birth defects may affect 5-8% of all babies born each year[6].

In a study of rural black South African neonates, malformations of the central nervous system were those noted most frequently, with an incidence of 4.33 per 1000 births, followed by musculoskeletal abnormalities and chromosomal defects[5]. In this study, chromosomal disorders were found to have an incidence of 2.75 per 1000 live births. Down's syndrome, which has a worldwide incidence of 1 in 700 births, for singleton pregnancies[7], was found in 2.1 per 1000 live births among black neonates in rural areas[5].

TABLE 1.1 BIRTH PREVALENCE AND OUTCOMES OF BIRTH DEFECTS IN POPULATIONS OF NORTH EUROPEAN ORIGIN. (Adapted from Christianson, *et al*[8])

Group of Conditions	Birth prevalence /1000	Early Mortality /1000	Chronic problems /1000	Cure /1000
Congenital malformations	36.5	8	8.8	19.7
Chromosomal disorders	3.8	1.3	2.4	0.1
Single gene disorders	12.3	7.1	3.8	1.4

The figures quoted in Table 1.1 show that congenital abnormalities, including chromosomal defects, have a higher prevalence in the Northern European populations when compared to third world countries, such as rural South Africa. This may be related to better postpartum detection facilities.

Assisted reproductive techniques also increase the burden of prenatal diagnostics. In first world countries, twin pregnancies also account for 1.3 per 100 births and this rate is increasing, due to the use of assisted reproductive technology.[9]

The outcome of infants born with congenital abnormalities depends on the severity of the congenital disorder, as well as the level of development of health services. In low-resource settings most affected infants die undiagnosed, but as services become available an increasing proportion are cured, or survive with chronic disabilities such as Down's syndrome, neural tube defects, or mental retardation.[10] It was estimated in 1983 that R 1 billion was spent on the management of congenital or genetic conditions. Inflation, increase in population, better adult education, and improved survival, have led to a quadrupling of the cost incurred.[5]

It is the parents of congenitally abnormal children who bear the greatest burden.
Caring for a congenitally abnormal or mentally retarded child is expensive and emotionally traumatic to both parents. Chromosomal abnormalities such as Down's syndrome may prove to be a greater burden than those with lethal abnormalities, since many of these children reach adulthood and are unable to support themselves. They will then become a social and financial burden for close relatives.

1.1.2 CALCULATION OF RISK FOR CHROMOSOMAL DISORDER

A woman's risk of having a congenitally abnormal baby is determined by her *a priori* risk, which in turn is dependant upon: maternal age, the duration of the pregnancy and a history of previous congenital abnormalities. Every time a test is performed, this background risk is

multiplied by the test factor or likelihood ratio, from which a new risk is then derived, and this becomes the *a priori* risk for the next test.[7] This pattern of screening is referred to as sequential screening. The components of sequential screening are: maternal age; biochemistry screening; nuchal translucency screening; ductus venosus flow; and the presence of the nasal bone.

1.1.2.1 MATERNAL AGE AND GESTATIONAL AGE

It is well established that the incidence of chromosomal abnormalities increases proportionately with an increase in the maternal age.[7,11,12,13] The evidence to support maternal age related risk of Trisomy 21 comes from a Survey in the South of Belgium[14] where each neonate was examined for Trisomy 21, and in a Swedish survey[15] where information was confirmed using birth records and other resources. The latter 2 surveys established, without a doubt, the proportionate risk between advanced maternal age and the incidence of Trisomy 21. Figure 1-1[7] reflects that Trisomy 21 is noted with a greater frequency than Trisomies 18 and 13 respectively, in association with advancing maternal age. The risk of Turner's syndrome and Triploidy remains constant with age (Figure 1-1).

Fetuses with chromosomal abnormalities are more likely to die in utero than normal fetuses and hence the risk decreases with advancing gestation (Figure 1-2).[7] To calculate the relative risk of Trisomy 21 at different gestations, Snijders, *et al*[13], used data from 57 614 women who had fetal karyotyping at 9-16 weeks gestation for the sole indication of maternal age of 35 years or more.[13] They then calculated the expected number of Trisomy 21 cases for each gestational age subgroup, by comparing the maternal age distribution and the maternal age

related risk for Trisomy 21. The derived prevalence of Trisomy 21 by maternal age and gestational age is reflected in Table 1.2.

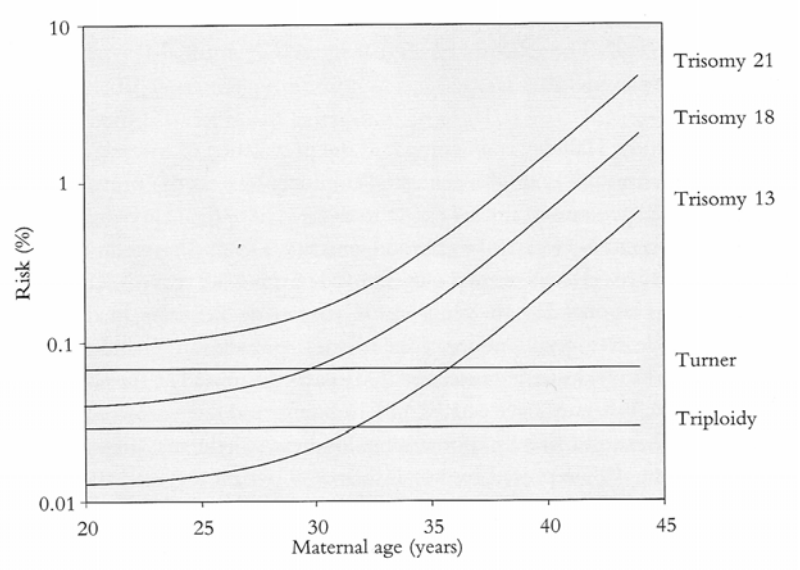


Figure 1-1 MATERNAL AGE-RELATED RISK FOR CHROMOSOMAL ABNORMALITIES[7]

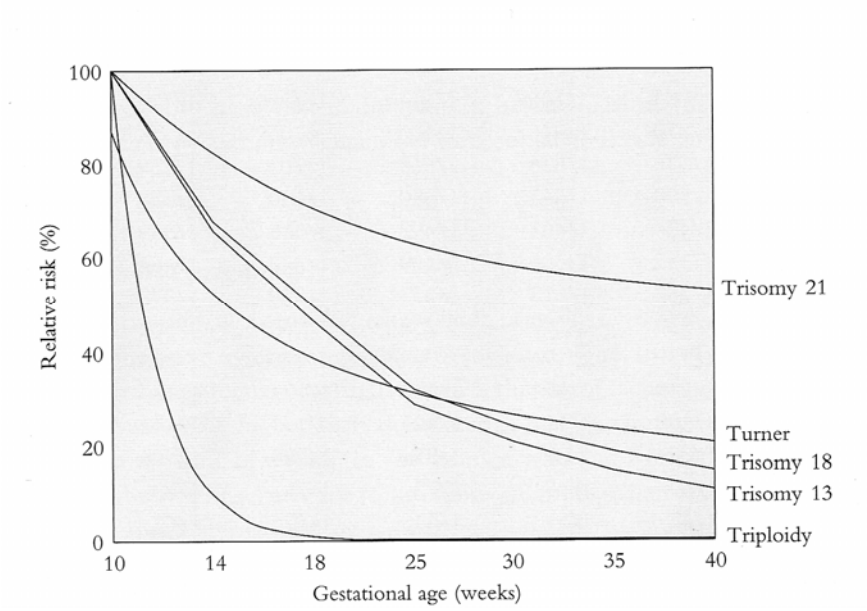


Figure 1-2 GESTATIONAL AGE-RELATED RISK FOR CHROMOSOMAL ABNORMALITIES[7]
(The lines represent the relative risk according to the risk at 10 weeks of gestation)

Table 1.2 PREVALENCE OF TRISOMY 21 BY MATERNAL AGE AND GESTATIONAL AGE. (Adapted from Snijders, *et al*[13])

Maternal age (years)	Gestational age (weeks) 10	12	14	16	20	40
20	1/983	1/1068	1/1140	1/1200	1/1295	1/1527
25	1/870	1/946	1/1009	1/1062	1/1147	1/1352
30	1/576	1/626	1/668	1/703	1/759	1/895
34	1/287	1/312	1/333	1/350	1/378	1/446
35	1/229	1/249	1/266	1/280	1/302	1/356
36	1/180	1/196	1/209	1/220	1/238	1/280
37	1/140	1/152	1/163	1/171	1/185	1/218
38	1/108	1/117	1/125	1/131	1/142	1/167
39	1/82	1/89	1/95	1/100	1/108	1/128
40	**1/62**	**1/68**	**1/72**	**1/76**	**1/82**	1/97

1.1.2.2 PREVIOUS CHROMOSOMAL ABNORMALITIES

Nicolaides, *et al* stated that in a study of 2054 women who had a previous pregnancy with Trisomy 21, it was found that the risk of recurrence in the subsequent pregnancy was 0.75% higher than the maternal and gestational age-related risk for Trisomy 21 at the time of testing.[7] Similar recurrence rates have been quoted for Trisomy18.[7,16] Hence, this influences the a *priori* risk by a factor of 0.75.[7]

1.1.3 NUCHAL TRANSLUCENCY

1.1.3.1 HISTORICAL ASPECTS

In a paper published by Langden Down: "Observations of an ethnic classification of the idiots", he described the skin of babies with Trisomy 21 as being deficient in elasticity and giving the appearance of being too large for the body.[17]

Langden Down was the first to describe the phenotypic appearance of Trisomy 21 babies and hence the appellation Down's syndrome, which is used interchangeably with the term Trisomy 21.

In 1959 Lejeune, *et al* were the first scientists to attribute a congenital birth defect to a chromosomal abnormality (Trisomy 21).[18]

Down's description of the appearance of the skin of babies with Trisomy 21, was the basis for the ultrasonographic observation, made more than a century later, by Sazbo and Gellen[19], where nuchal fluid accumulation in Trisomy 21 fetuses were first detected via transvaginal ultrasonography. Over a period of 3 years, Sazbo and Gellen[19], examined 7 fetuses with Trisomy 21 and confirmed these findings in all of them. The typical ultrasonographic appearance of accumulation of nuchal subcutaneous fluid can be seen in Figure 1-3.



FIGURE 1-3 ULTRASOUND PICTURE OF A 12 WEEK FETUS WITH TRISOMY 21. (Distance between calipers demonstrates increased nuchal translucency thickness.) Image kindly provided by Prof Ermos Nicolaou, University of the Witwatersrand.

1.1.3.2 NUCHAL TRANSLUCENCY OR CYSTIC HYGROMA?

In 1994, Trauffer, *et al*[20], stated that a nuchal cystic hygroma found during second trimester ultrasound scan, has a strong association with aneuploidy, most commonly 45 X, but also Trisomies 21 and 18. Trauffer, *et al* further stated that when the Karyotype was normal, the cystic hygroma may signal the presence of a single gene defect such as Noonan syndrome. For many years this appearance of subcutaneous thickening of the skin behind the neck, was referred to as a cystic hygroma. In the second trimester the association between subcutaneous skin thickening and aneuploidy is recognized. However, the term nuchal translucency arose as a delineation of the first trimester nuchal fluid accumulation from the second trimester skin thickening.

1.1.3.3 FETAL NUCHAL FLUID- PHYSIOLOGICAL OR PATHOLOGICAL?

In 1976, Nishimura H and Okamoto N[21], found that these subcutaneous fluid collections were present in 40% of embryos at less than 10 weeks, and had resolved a week later. Chervenak, *et al*[22], stated that pathological fluid collections may occur when there is congenital dysplasia of the lymphatic system and failure of its connection with the internal jugular system.

In 1990 lesions were considered to be pathological when they were greater than 5 mm in depth.[23] Wilson, *et al*[24], reported on the findings of 43 pregnancies, where the embryos or fetuses had increased nuchal fluid prior to 17 weeks. They concluded from their study that nuchal fluid may be physiological or pathological; however recognition of those patterns which are pathological is important to allow invasive prenatal assessment for chromosome evaluation while minimizing the risk of post-procedural spontaneous loss of chromosomally normal fetuses.[24]

1.1.3.4 THE FETAL MEDICINE FOUNDATION PROJECT - NUCHAL TRANSLUCENCY AND ANEUPLOID FETUSES

In August 1998, the publication by Snijders, *et al*[1] reported on 100 311 singleton pregnancies with live fetuses, which were examined by means of ultrasonography at a median gestation of 12 weeks. Ninety six thousand and one hundred and twenty seven fetuses had either prenatal or postnatal karyotyping performed, or were assessed by examination of the neonate for dysmorphic features.

The findings of this UK Multicenter project changed the approach to prenatal screening for Trisomy 21 as well as for other abnormalities.

This multicentre project identified 326 fetuses with Trisomy 21 and 325 fetuses with other chromosomal abnormalities. Snijders, *et al*[1] reported that the fetal nuchal translucency thickness was above the 95th percentile for nuchal translucency nomograms as derived from crown-rump length, in 4.4% of the 96 476 normal pregnancies. These authors found that the estimated risk of Trisomy 21, based on the maternal age and the fetal nuchal translucency thickness, was 1:300 or higher in 8.3% of normal pregnancies; 82.2% of those with Trisomy 21; and 77.8% of those with other chromosomal defects.

Therefore, for a cut-off estimated risk of Trisomy 21 of 1:300, the sensitivity was 82.2%, the false positive rate was 8.3%, the positive predictive value was 3.2% and the negative predictive value was 99.9%.[1] When adjusted to achieve a 5% false positive rate, the sensitivity fell to 77%.[1] The various aneuploidies which were detected are depicted in Table1.3.

TABLE 1.3 NUMBER OF PREGNANCIES WITH NUCHAL TRANSLUCENCY THICKNESS ABOVE THE 95th CENTILE AND THE ESTIMATED RISK FOR TRISOMY 21 OF 1:300 OR GREATER.(Adapted from Snijders, *et* al[1])

Fetal karyotype	Total	Number with NT thickness > 95th percentile	Number with estimated risk 1:300 or more
Normal	95476	4209 (4.4%)	7907 (8.3%)
Trisomy 21	326	234 (71.8%)	268 (80.2%)
Other chromosomal abnormalities			
Trisomy 18	119	89 (74.8%)	97 (81.5%)
Trisomy 13	46	33 (72%)	37 (80%)
Turner's syndrome	54	47 (87%)	48 (89%)
Triploidy	32	19 (59%)	20 (63%)
Other*	74	41 (55%)	51 (69%)
Total	**96127**	**4767 (4.9%)**	**8428 (8.8%)**

NT= nuchal translucency.
*Deletions, partial Trisomies, unbalance translocations, sex chromosome aneuploidies.

1.1.3.5 NUCHAL TRANSLUCENCY AND EUPLOID FETUSES

Since the initiation of the UK multicentre project there have been several reports of defects and syndromes in chromosomally normal fetuses with increased nuchal translucency thickness at 10-14 weeks gestation.[25,26,27,28] Souka, *et al*[25] reported on 4116 singleton, chromosomally normal pregnancies with fetal nuchal translucency thickness above the 95th percentile for crown rump length, at a median gestation of 12 weeks. They found an overall outcome of 3885 live births of infants who survived the neonatal period, 38 neonatal deaths, 74 spontaneous abortions or intra-uterine deaths and 77 terminations at the request of the parents because of fetal abnormalities detected by ultrasonography (Table 1.4).[25]

Cardiac abnormalities are also common and although most of the ultrasonographic features may be detected by specialist fetal echocardiography at the18-22 week scan, many abnormalities are undetected at routine antenatal ultrasonography.[28]

Data published by Zosmer, *et al*[28]**,** revealed that there is a high association between increased nuchal translucency and major cardiac defects. They stated that where the nuchal translucency measurement was greater than 3.5mm, the prevalence of cardiac defects was increased tenfold.

TABLE 1.4 FETAL ABNORMALITIES AND GENETIC SYNDROMES IN CHROMOSOMALLY NORMAL FETUSES WITH INCREASED NUCHAL TRANSLUCENCY THICKNESS AT 10-14 WEEKS GESTATION ACCORDING TO NUCHAL TRANSLUCENCY THICKNESS (mm) (Adapted from Souka, *et al*[25])

Fetal abnormality	Fetal nuchal translucency thickness (mm)					Pregnancy outcome			
	<3.5	3.5-4.4	4.5-5.4	5.5-6.4	≥6.5	TOP	IUD	NND	Alive
Anencephaly	4	1				5			
Encephalocoele	3				1	4			
Ventriculomegaly	6					5			**1**
Dandy Walker cyst	1					1			
Holoprosencephaly	1					1			
Microcephaly	1								**1**
Facial cleft	2								**2**
Cystic hygroma	1								**1**
Major cardiac defects	12	12	6	3	10	19	6	3	**15**
Diaphragmatic hernia	4	1	3	1		1		5	**2**
Exomphalos	2	3	1	1		5	1		**1**
Gastroschisis		1						1	
Bowel obstruction	2								**2**
Duodenal atresia		1							**1**
Hydronephrosis	2	2	1			1			**4**
Multicysic kidneys	4					3			**1**
Polycystic kidneys					1	1			
Renal agenesis	1	1				1			**1**
Megacystis	7	1				2	2		**4**
Spina bifida	3	1				2	1		**1**
Kyphoscoliosis				1		1			
Diastomatomelia	1								**1**
Talipes	**10**	**4**	**1**			**1**			**14**

TOP=Termination of pregnancy

IUD=Intrauterine death

NND=Neonatal Death

However, because of technical limitations and uncertainty concerning pathophysiology of congenital cardiac abnormalities, Zosmer, *et al*[28] regard a second follow up scan at 20 weeks, as necessary in cases with apparently normal echocardiography at 14-16 weeks.

1.1.3.6 THE OPTIMAL GESTATIONAL AGE TO EXAMINE FETAL NUCHAL TRANSLUCENCY

In both normal and abnormal fetuses, the nuchal translucency measurements increase significantly with increasing gestation.[29] Braithwaite, *et al*[29], demonstrated that an increase in the mean crown rump length measurements from 44.8mm to 70.1 mm resulted in a mean increase in the nuchal translucency of 0.66 mm. Hence a single cut off value becomes inappropriate. There is a need for consistent results which are precise and repeatable for general population screening. Hence normograms for nuchal translucency were developed in relation to crown rump length measurements.

It is best to review nuchal translucency at a crown rump length of between 45mm and 84mm or a gestation of 11 to 14 weeks.[7] The reason for the upper cut off limit being set at 13 weeks and 6 days, is to allow women with abnormal fetuses the option of an earlier and safer termination of the pregnancy.

1.1.4 SCREENING THE GENERAL POPULATION

Roberts, *et al*[30] stated that if nuchal translucency ≥ 3mm were used as an indicator for karyotyping, 6% of the normal pregnant population would screen positive, but the percentage would vary greatly depending on the gestational age profile of the screened population. In an unselected population, the value of nuchal translucency measurement as a screening test for Down's syndrome could be diminished.

1.1.5 THE ANATOMICAL SURVEY

Braithwaite, *et al*[31] examined 298 consecutive women attending a routine gestational-dating scan clinic at between 12 and 14 weeks' gestation, and offered high resolution ultrasonographic examination of the fetus via the trans-abdominal and trans-vaginal approach. Complete surveys of fetal anatomy were possible in 72% of women with trans-abdominal sonar, 82% with trans-vaginal sonar and 95% by a combination of the 2 scan modes.[31]

Thus, using the anatomical survey proposed by these workers, it is possible to perform a complete anatomical assessment in 95% of fetuses by combining the 2 scan modes at 12-13 weeks of gestation.(Table 1.5)

TABLE 1.5 CRITERIA NECESSARY FOR ADEQUATE VISUALIZATION OF FETAL ORGANS[31]

Organ	Criteria necessary for adequate visualization
Head	Complete cranium, septum pellucidum, thalamus, choroid plexi, cerebellum and ventricles
Face	Correct position of mandibles, maxillae and orbits
Heart	Four chamber view, symmetrical ventricles and atria
Diaphragm	Hypoechoeic interface between abdomen and thoracic cavities
Stomach	Single, hypoechoic structure in the left upper abdomen
Abdominal wall	Normal cord insertion and abdominal wall
Kidneys	Visualization of the cortex and pelvis of both kidneys
Bladder	Hypoechoic structure anteriorly in the midline of the pelvis
Spine	Complete vertebrae seen in both transverse and coronal planes with normal overlying skin
Extremities	Visualization of long bones, correct posture of hands and feet

1.1.6 BIOCHEMISTRY AND SEQUENTIAL SCREENING

First trimester biochemistry screening employs the use of assays of serum pregnancy associated plasma protein A and free beta subunit of human chorionic gonadotrophin levels. This may detect 60% of Trisomy 21 fetuses at a screen positive rate of 5%.[32] The additional cost implications according to the South African national health reference price list is R393.20 per test. In order to achieve a sensitivity of 97%, one would have to incorporate biochemistry screening into each test performed.[7] However, in an outcomes analysis of five prenatal screening strategies for Trisomy 21 in women younger than 35 years[33], it was found that sequential screening was the most cost-effective screening strategy for Trisomy 21.

1.1.7 DIAGNOSIS BY INVASIVE TESTING

No screening test is effective unless a suitable diagnostic procedure is available to validate findings. It has been suggested that routinely offering invasive testing to women over the age of 35 without biochemical testing should be abandoned.[34] Chorionic villus sampling is the invasive procedure of choice in determining the karyotype of a fetus that screens positive in the first trimester. The advantage of earlier diagnosis is that it reduces the psychological impact of termination of pregnancy in women with abnormal fetuses, since fetal movements have not yet been felt. Earlier diagnosis also lends itself to an earlier and safer form of termination of pregnancy as opposed to a second trimester termination. With increasing experience, the complication rate of CVS versus amniocentesis equalizes.[35]

1.1.7.1 MATERNAL ACCEPTANCE OF CHORIONIC VILLUS SAMPLING

There are various reasons why women decline or accept invasive testing. These reasons range from understanding or not understanding the fetal condition to religious reasons. Some may find even a minimal risk of a fetal abnormality unacceptable.

In a study by Chasen, *et al*[36], on 4029 women, it was found that higher rates of nuchal translucency screening were associated with lower rates of chorionic villus sampling and it was deduced that first trimester screening may lead to reduced rates of invasive testing and fewer losses of normal pregnancies.

1.1.8 IMPROVING THE SENSITIVITY OF FIRST TRIMESTER SCREENING

Screening for Down's syndrome continues to improve. Recent studies have shown that sonographic markers such as the absence of a nasal bone and abnormal ductus venosus flow can enhance the sensitivity of screening.[37,38,39]

1.1.8.1 SONOGRAPHIC ASSESSMENT OF DUCTUS VENOSUS FLOW

The Doppler gate is placed in the ductus venosus between the umbilical venous sinus and the inferior vena cava. In Figure 1-4, it will be seen that there is biphasic pulsatile flow with constant forward flow, and the troughs of flow during atrial contraction also demonstrate forward flow.[40] Forward biphasic pulsatile ductus venosus flow is normal, whilst reversed flow at the time of atrial contraction has been associated with aneuploidy and congenital heart defects.[38]

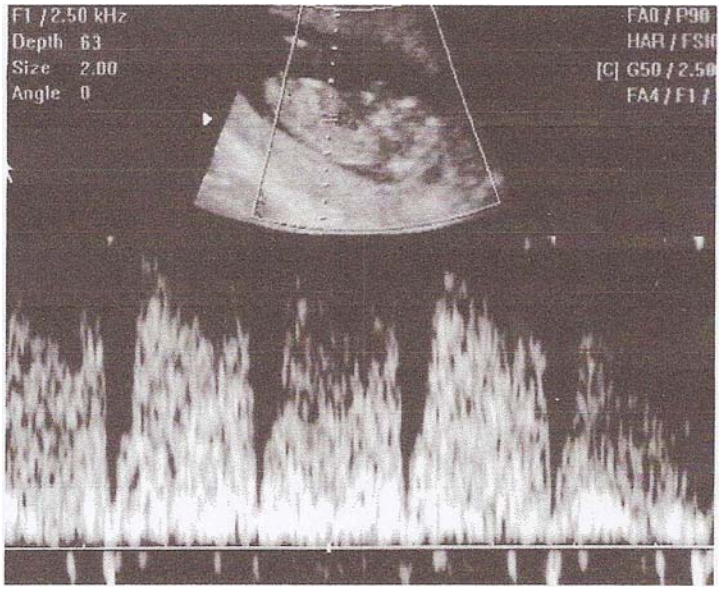


FIGURE 1.4 DUCTUS VENOSUS FLOW VELOCITY WAVEFORM IN A NORMAL 13 WEEK FETUS. Image kindly provided by Prof Ermos Nicolaou, University of the Witwatersrand

1.1.8.2 SONOGRAPHIC ASSESSMENT OF THE NASAL BONE [41]

A mid-sagittal view of the fetal profile is obtained with the ultrasound transducer being held parallel to the longitudinal axis of the nasal bone. The angle of insonation is crucial because the nasal bone will seldom be visible when the longitudinal axis of the bone is perpendicular to the ultrasound transducer. In the correct view, there are 3 distinct lines.

The first 2 lines, which are proximal to the forehead, are horizontal and parallel to each other, resembling an ‘‘equal sign.’’ The top line represents the skin and the bottom line, which is thicker and more echogenic than the overlying skin, represents the nasal bone (Figure 1-5). A third line, which is almost in continuity with the skin but at a higher level, represents the tip of the nose.

When the nasal bone line appears as a thin line, less echogenic than the overlying skin, it suggests that the nasal bone is not yet ossified and is classified therefore as being absent (Figure 1-6).

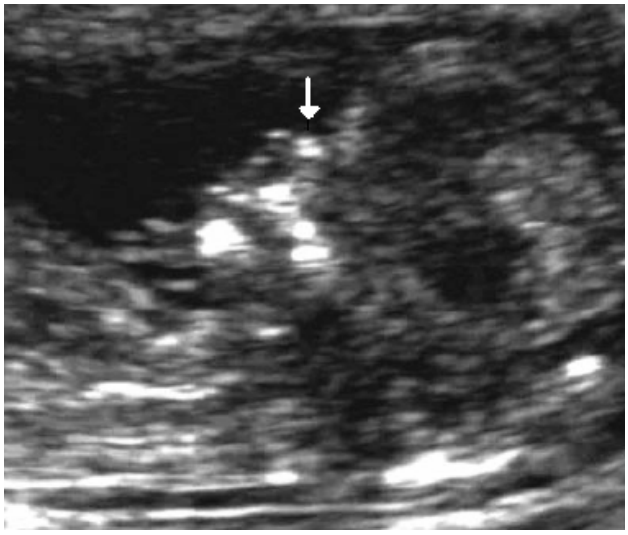


FIGURE 1-5 NASAL BONE IN A CHROMOSOMALLY NORMAL FETUS AT 12 WEEKS. Image kindly provided by Prof Ermos Nicolaou, University of the Witwatersrand



FIGURE 1-6 ABSENT NASAL BONE IN A TRISOMY 21 FETUS AT 12 WEEKS. Image kindly provided by Prof Ermos Nicolaou, University of the Witwatersrand

Including sonographic screening for the nasal bone and tricuspid regurgitation into the first trimester screening programme would, for a fixed false-positive rate of about 5%, increase the detection rates from about 75% and to 97%.[42]

1.1.9 MULTIPLE PREGNANCIES

1.1.9.1 TYPES OF MULTIPLE PREGNANCIES

Multiple pregnancies usually result from either fertilization of multiple ova or from splitting of one embryonic mass. The former is termed polyzygotic multiple pregnancies and the latter, monozygotic twinning. In polyzygotic pregnancies each fetus has a separate placenta while in monozygotic pregnancies, the placenta is often shared. The incidence of twin pregnancies is 2% of all pregnancies, with 2/3 being dizygotic and 1/3 being monozygotic. The incidence of monozygotic twins is constant and does not vary with age, parity and race but is increased following in vitro fertilization. The incidence of dizygotic twin pregnancies, on the other hand, is influenced by age, race and parity.

1.1.9.2 SCREENING FOR ANEUPLOIDY IN TWIN PREGNANCIES

Screening for aneuploidy in twins presents a complex array of problems since one has to determine if aneuploidy is present and, in particular, which fetus is affected. If a fetus is affected, then even further care needs to be taken to ensure that should a fetocide be required, that the correct fetus is terminated.

The prenatal risk assessment for twin pregnancies is more complex than for singleton pregnancies. Prior to the advent of first trimester nuchal translucency screening, the only parameter available for risk screening was age. Biochemical screening using multiples of

median, currently has no place in twin pregnancies since the normograms extrapolated from singleton pregnancies are affected by the zygosity of the twin pregnancy.[9] With technological advances in the field of infertility and in-vitro-fertilization, the incidence of multiple pregnancies continues to rise.

In a study by Sebire, *et al*[43], it was found that the sensitivity of fetal nuchal translucency thickness in screening for Trisomy 21 among twin gestations was similar to that in singleton pregnancies. Specificity was lower, because translucency was also increased in association with an early onset of twin-twin transfusion syndrome in chromosomally normal monochorionic twin pregnancies.

Whilst first-trimester nuchal translucency screening provides fetus-specific risk estimates, a positive screening test presents a dilemma regarding the decision as to which fetus is abnormal. To undertake an invasive diagnostic test would place both fetuses at risk.[9]

Sebire, *et al*[44] presented data on using the results of nuchal translucency as a guide to patients' in their decision regarding having either a CVS in the first trimester or an amniocentesis in the second trimester.

An added advantage of first trimester nuchal translucency screening in twin pregnancies, is the determination of chorionicity.

1.2 PURPOSE OF THE STUDY

This study aims to assess a first trimester screening programme which incorporates maternal age derived background risk, nuchal translucency measurement, and the presence of a nasal bone in a tertiary care institution. Following the literature review, it is evident that advances in first trimester screening have improved the sensitivity of screening. However, there is limited data on its use in a predominantly black South African population. Expense, unlike in first world practice, is the most important limitation in South Africa.

This study evaluates the quality of care provided with the use of a first trimester screening programme without biochemical screening, in a population that is primarily black.

1.3 SETTING

The Chris Hani Baragwanath Hospital is both a secondary and tertiary referral centre, that serves predominantly the surrounding health care clinics, and primary and secondary hospitals in the south of Johannesburg. More distant hospitals may refer patients for specialist opinion and management. The domain of referral includes the entire Sowetan district which comprises a predominantly black population together with a few people of mixed ethnicity.

Being a tertiary care institution, most patients are referred to the Chris Hani Baragwanath hospital complex, for attention to medical conditions that cannot be addressed at primary or secondary care level. Not all the health care clinics however have antenatal facilities, and hence approximately 30% of women attended to in the antenatal clinic attend of their own volition.

Even in this low socio-economic community patients, including those referred from primary and secondary care facilities, may need to provide their own means of transport to health care facilities. State provided transport is only available to patients with acute medical conditions. Although it is difficult to commute, many patients seem to be willing to travel the distance because of the perception of being cared for in a "bigger and better" hospital.

Referred patients are received and reviewed in the antenatal clinic at the Chris Hani Baragwanath Hospital, where they are interviewed and examined by doctors. After initial evaluation of the patient's condition, every patient is referred to the fetal medicine unit for a baseline sonographic evaluation of the fetus, unless the pregnancy is already assessed to be term. The policy of the fetal medicine unit is to offer every pregnant woman at least one ultrasound scan in pregnancy.

At the Fetal Medicine Unit, level 3 sonographers perform the initial ultrasonographic assessment of fetuses. Thereafter, if a fetus is found to be less than 14 weeks gestation or 84mm in crown rump length, the patient is referred to the first trimester screening clinic. On arrival at the first trimester screening clinic, each patient is counseled by trained genetic counselors about the use of first trimester nuchal translucency screening for congenital abnormalities, and the patients *a priori* risk. First trimester screening is then only undertaken after obtaining verbal informed consent of the patient.

After the nuchal translucency measurement has been performed, the data is entered into a software programme provided by the Fetal Medicine Foundation in London, and a new *a priori* risk or adjusted risk is determined.

The patient is then informed of her risk. The majority will be reassured by a reduction in risk and will then opt to forego invasive diagnostic testing, in favor of a 20 weeks ultrasound assessment to review the fetal anatomy for structural markers of aneuploidy. Although only patients with a risk of greater than 1:300 are classified as screen positive and are offered invasive diagnostic testing via chorionic villus sampling, strict measures are not adhered to and occasionally, patients that screen negative may insist on having invasive testing performed. This occurs most frequently in the event of there having been an abnormality in a previous pregnancy.

The patient is informed by the genetic counselors that, should the baby have any abnormalities after birth, they should return to see the genetic counselor at the pediatric clinic. Attached to every antenatal record card is a printed copy of the first trimester screen, so that the doctors caring for the patient at the time of delivery are aware of the findings.

Despite the expense, the majority of these patients manage to find transport back to the hospital for a sonographic review at 20 weeks.

1.4 OBJECTIVES

1. To determine the effectiveness of nuchal translucency screening in predicting aneuploidy in a South African population at a tertiary care institution.
2. To determine the types of aneuploidy associated with a positive screen in a South African population.
3. Cost evaluation to determine the cost effectiveness of the screening programme.

The findings in all women who had first trimester nuchal translucency screening will be reviewed. The outcome at birth will be compared to the predicted condition.

1.5 STUDY DESIGN

This will be a descriptive study of the findings observed.

2. MATERIALS AND METHODS

2.1 STUDY SAMPLE-Study population, timing and sampling

2.1.1 A retrospective analysis was performed on all records of patients who had first trimester nuchal translucency screening performed at the Chris Hani Baragwanath Hospital fetal medicine unit between July 2003 and July 2005.

2.1.2 The study population comprised patients that had been attended to at the Chris Hani Baragwanath hospital antenatal clinic, and were then referred to the Fetal Medicine Unit for first trimester screening.

2.1.3 The antenatal records of all patients who had received first trimester screening during the period under review were retrieved and reviewed. There are no exclusion criteria.

2.1.4 In order to determine the number of undiagnosed abnormalities in the group, all babies were examined by a paediatrician at birth to detect and describe dysmorphic features. In addition, babies attending the paediatric clinics were reviewed and assessed to determine the incidence of late presentation and sequelae.

2.2 DATA COLLECTION

The patients were identified by performing a computer search of the fetal medicine unit database for all women who had received first trimester screening between July 2003 and July 2005.

This database was provided by the Fetal Medicine Foundation. All of the names are stored in alphabetical order, but can be retrieved chronologically. The relevant hospital numbers of patients, who underwent first trimester screening in the CH Baragwanath complex, were

obtained. Anonymity of patients was maintained by use of a study number. A study number was assigned to each case. This number was then used to retrieve, review and record the following variables: maternal age, last normal menstrual period, previous chromosomal abnormality, ethnicity; ultrasound parameters included: fetal biometry, nuchal translucency measurement, abnormalities such as cranial defects, spinal defects, abdominal wall defects, and limb anomalies; results of fetal karyotype analysis and final outcome of pregnancy.

In order to determine the number of undiagnosed abnormalities in the screen negative group, all the babies were examined at birth by a paediatrician to detect and describe dysmorphic features. In addition to this, the medical records of babies who subsequently attended the paediatric clinics, were reviewed and assessed to determine the incidence of late presentation and sequelae.

Please refer to **APPENDIX A**.

There were no exclusion criteria.

2.3 THE MEASUREMENT OF NUCHAL TRANSLUCENCY

2.3.1 EQUIPMENT

The ultrasonographic scans were carried out on the Siemens G50 and the Medison Accuvix XQ machines, which provide high resolution ultrasonography. The ultrasonographic scans were performed trans-abdominally using a curvilinear 3.5MHz transducer or trans-vaginally using a 7 MHz transducer.

2.3.2 INTER-OBSERVER VARIABILITY

The measurements of nuchal translucency were performed by 2 doctors who had received the Fetal Medicine Foundation certificate of competence in the theory and practice of the 10-14 week scan.

2.3.3 SONOGRAPHIC CRITERIA TO MAXIMIZE QUALITY OF NUCHAL TRANSLUCENCY SCREENING[40]

The following fetal Medicine foundation Criteria were used to achieve uniformity of the results between these two doctors:

- **a.** Transabdominal or transvaginal approach should be left to the sonographer's discretion, based on maternal body habitus, gestational age and fetal position.
- **b.** Gestation should be limited to between 10 to 14 weeks.
- **c.** Crown rump length should be limited to between 45 and 84 mm.
- **d.** The fetus should be examined in the midsagittal plane.
- **e.** The fetal neck should be in a neutral position.
- **f.** The magnification should be such that the fetus occupies at least three quarters of the image. Essentially the magnification should be increased to the extent that each increment in the distance between calipers should be only 0.1 mm.
- **g.** Care is taken to distinguish between fetal skin and amnion because, at this gestation, both structures appear as thin membranes.
- **h.** The maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine should be measured by placing the calipers on the lines as shown in Figure 2-1.

i. Calipers should be placed in an on to on position. (Figure 2-2)

j. Calipers should be placed perpendicular to the fetal body axis.

k. During the scan three measurements are taken and the maximum recorded.

l. At least 20 minutes should be dedicated to the nuchal translucency measurement before abandoning the attempt as failed.



FIGURE 2-1 MIDSAGITTAL SECTION OF FETUS AT APPROPRIATE MAGNIFICATION. Image kindly provided by Prof Ermos Nicolaou, University of the Witwatersrand.

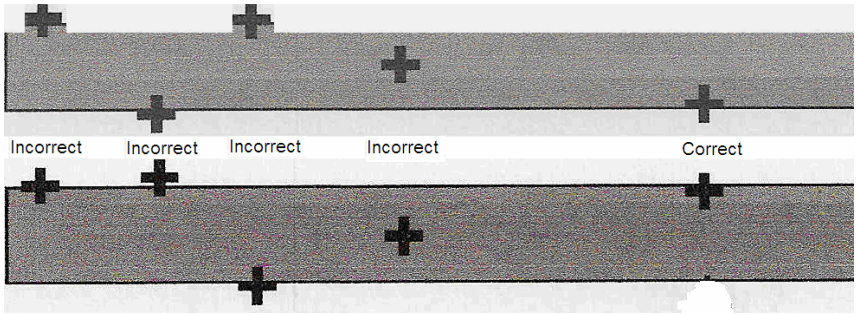


FIGURE 2-2 CORRECT POSITIONING OF CALIPERS.[7]

2.4 CALCULATION OF RISK

The sonographic findings of the 10-14 week scan, as well as the demographic data, were then entered into the software programme provided by the Fetal Medicine Foundation and used to calculate the adjusted risk. A screen was considered to be positive if the adjusted risk was greater than 1:300 and negative if the risk was <1:300.

2.5 EVALUATION OF THE COST OF SCREENING

In order to estimate cost the South African national health reference price list was used. The unit price of each process was taken into account.

TABLE 2.1 NATIONAL HEALTH REFERENCE PRICE LIST

Service Provided	Cost (Rands.cents)
Cell culture (amniotic cells)	**321.50**
Cell culture (chorionic villi)	**429.00**
Cytogenetic analysis	**1756.20**
Total cost of a first trimester screen	**2359.70**
Total cost of a second trimester screen	**2426.70**

2.6 ANALYSIS OF RESULTS

The results will be analyzed using Epi-Info 6.04 software and the *p* value will be set at <0.05 to determine statistical significance. All patients' in whom the outcome of the pregnancy was not available, were be excluded from sub analyses. For normally distributed data, the Analysis

of Variance (ANOVA) was used and the mean and standard deviation were recorded. The Kruskal Wallis test was used for non parametric data and the median and range were recorded. The study was commenced after Ethics approval was obtained. Protocol number: M041108. **(Appendix B)**

3. RESULTS

A total of 428 patients had first trimester screening during this period. Thirteen patients (3%) were lost to follow up and were excluded from sub-analysis.

3.1 FIRST TRIMESTER SCREENING OUTCOMES

Of the 415 cases that were analyzed, 59 patients screened positive and 356 screened negative. Black patients comprised 77.6% of the total, with 14% Colored, 6% White and 2.1% Indian.

3.2 FIRST TRIMESTER SCREENING CHARACTERISTICS

Twenty six percent of women were older than 35 years. The results in Table 3.1 show that there is no significant difference between the mean ages of women who screened positive and those who screened negative.

The first trimester screening characteristics of fetuses (Table 3.1) indicates that the crown rump length measurements of fetuses of women who had screened positive, were significantly shorter than fetuses of women in whom a negative screen result was obtained. The latter finding may have been due to possible early onset of intra-uterine growth restriction.
Only 46% of women in the screen negative group and 23% of women in the screen positive group could recall their last normal menstrual period.

TABLE 3.1 FIRST TRIMESTER SCREENING CHARACTERISTICS

Variable	Screen Negative		Screen Positive		P-value
	n=356	Range	n=59	Range	
Age of patient (yrs)	30.1	12-49	31	23-43	0.466
Gestational age (weeks.days)	13.2	11.1-14.0	12.5	11.2-13.6	<0.01
Crown Rump length (mm)	69.4	65-84	64.7	47.0-83.2	0.01
Fetal Heart Rate (b/min)	164	146-180	170	147-185	0.34
Nuchal Translucency	1.8	1.0-2.5	3.65	1.7-9.6	<0.01

3.3 CHORIONIC VILLUS SAMPLING

Table 3.2 summarizes the outcomes of screened patients in whom chorionic villus sampling was performed and those who elected not to have the procedure. Of the 59 patients who screened positive, 24 elected to have chorionic villus sampling (CVS) This resulted in the detection of 5 chromosomal abnormalities (2 Trisomy 21; 1 Trisomy13; 1 Trisomy 18; 1 Turner's syndrome), 1 single gene defect (Tay-Sach's disease).

TABLE 3.2 SUMMARY OF FINDINGS OF CHORIONIC VILLUS SAMPLING

Outcome of Screening	Total screened n=428	Chorionic Villus Sampling				Outcome			
		Unsampled	Sampled	Results		*Total Abnormal	TOP	IUFD	Alive
				Normal	Abnormal				
Positive	59	35	24	18	6	13	12	6	41
Negative	356	347	9	8	1	1	1	6	346**

TOP=Termination of pregnancy.

IUFD=Intrauterine fetal death.

*Total abnormal= total number of chromosomally and phenotypically abnormal babies born.

**The deficit of 3 babies was due to 1 postprocedural (CVS) loss and 2 stillbirths related to maternal conditions.

In addition to the CVS, the anatomical survey detected 2 fetuses with acrania, 2 multi-structural abnormalities, and 4 fetuses had multi-structural abnormalities that were characteristic of Trisomy 13, Trisomy 18, Trisomy 21 and Turner's syndrome respectively. The patient in whom a Trisomy 21 fetus was suspected, elected not to have a CVS, and decided to continue with the pregnancy. The remaining 12 patients, in whom abnormalities were detected, elected to have terminations of their pregnancy. There were 6 intrauterine fetal deaths in the remaining 46 patients who had screened positive. Five were due to pre-eclampsia and 1 was related to warfarin induced hydrocephalus.

Of the 356 patients who screened negative, 2 patients had an increase in the adjusted risk when the risk was compared to the background risk. Both of these patients were offered a CVS. One elected to have a CVS and a Trisomy 18 fetus was diagnosed. This patient elected to have a termination of pregnancy. The remaining patient gave birth to a baby with no phenotypic abnormalities. The reasons for a CVS in the remaining 8 patients included: a previously abnormal fetus, advanced maternal age, a history of recurrent miscarriages, and in one case, confirmation of paternity. The karyotype of all these fetuses was normal. In this group, there was one post-procedural pregnancy loss. The 6 intrauterine fetal deaths were related to maternal complications such as eclampsia, abruptio placentae and over-warfainization. The 2 fresh still births were largely due to maternal hypertensive complications that necessitated preterm delivery.

3.3.1 GENDER DISTRIBUTION DERIVED FROM FETAL KARYOTYPE RESULTS

Table 3.3 illustrates that male fetuses had a significantly higher false positive screen as well as a higher frequency of chromosomal or structural abnormalities.

TABLE 3.3 GENDER DISTRIBUTIONS DERIVED FROM KARYOTYPE RESULTS

Outcome	Male %	Female %	p-value
Normal n=20	70	30	<0.01
Abnormal n=14	64.3	35.7	<0.01

3.4 STRUCTURAL ABNORMALITIES DETECTED

Table 3.4 summarizes the abnormalities which resulted in a positive screen, together with those which were confirmed using CVS. One patient, in whom a Trisomy 21 fetus was diagnosed, was not able to accept the diagnosis of Trisomy 21, even after delivery of the baby. One patient in whom the anatomical survey suggested Trisomy 13 and one in whom Turner's syndrome was suspected, elected to have terminations of their pregnancies. The abnormal karyotype of these fetuses were confirmed after delivery. The patients in whom fetuses with multi-structural abnormalities were detected, as well as the patients with fetuses that had acrania, chose to terminate their respective pregnancies. After delivery, the karyotype of these fetuses were found to be normal.

TABLE 3.4 STRUCTURAL ABNORMALITIES DETECTED

Abnormality detected	First Trimester Screen	Chorionic Villus Sampling
Trisomy 21	**3**	**2**
Trisomy 13	**2**	**1**
Trisomy 18	**2**	**2**
Turner's Syndrome	**2**	**1**
Tay-Sach's Disease	**1**	**1**
Multi-Structural Abnormality	**2**	
Acrania	**2**	

3.5 TWIN PREGNANCIES

Of the 5 twin pregnancies that underwent first trimester nuchal translucency screening, none were found to have fetuses with aneuploidy. (Table 3.5)

TABLE 3.5 RESULTS OF FIRST TRIMESTER SCREENING IN TWIN PREGNANCIES

Means	Dichorionic n=5	Monochorionic n=4	P-value
Nuchal Translucency (mm)	1.4 (1.3-1.6)	2.1 (2.0-2.3)	<0.01
Maternal age (years)	25	26	0.45

Monochorionic twin pregnancies had a higher mean nuchal translucency measurement than dichorionic twin pregnancies, and this may have been related to an early onset of twin-to-twin transfusion syndrome.

3.6 EVALUATION OF THE FIRST TRIMESTER SCREENING PROGRAMME

Table 3.6 confirms that the first trimester screening programme was effective in terms of achieving a high sensitivity, specificity and positive predictive value.

TABLE 3.6 EVALUATION OF THE FIRST TRIMESTER SCREENING PROGRAMME

First Trimester Screening		%	95 % CI
Sensitivity		92.9	64.2-99.6
Specificity		88.6	84.9-91.4
Positive Predictive Value		22.2	12.7-35.1
Negative Predictive Value		99.7	98.2-100
False Positive Rate		11	8.9-15.4
CVS Uptake Rate	Overall*	7.9	5.6-11.0
	High Risk**	5.7	28.0-54.2

* Overall CVS uptake (Includes all patients who had a CVS)

†High Risk CVS uptake rate (Includes only patients who had a positive screen and elected to have a CVS performed)

3.7 EVALUATION OF COST EFFECTIVENESS

Table 3.7 compares the actual cost of the first trimester screening programme at the Chris Hani Baragwanath hospital (indicated by blue background) to the hypothetical cost of a second trimester screening programme in the same group of patients (indicated by a yellow background).

TABLE 3.7 COST EFFECTIVENESS OF THE CHRIS HANI BARAGANATH HOSPITAL SCREENING PROGRAMME

Screening programme	n	Percentage Trisomy 21 Detected	Procedure Offered	Invasive Procedure Uptake		Cost in Rands
				%	No	
MA > 35 years	108	50	Amniocentesis	26	108	**R 262 083.60**
[a]MA +NT+NB	59	100	CVS	7.9	33	**R 77 870.10**
[b]MA+NT+NB	59	100	CVS	5.7	24	**R 56 632.80**

MA=Maternal age

NT=Nuchal translucency screening

NB=Nasal bone screening

CVS=Chorionic villus sampling

%=Percentage

No=Number of patients

*=Cost evaluation of all patients who elected to have chorionic villus sampling

†=Cost evaluation which only incorporates high risk patients (adjusted risk of ≥ 1:300) who elected to have chorionic villus sampling

If amniocentesis were performed in all 108 patients in the second trimester, only 50% of the fetuses with Trisomy 21 would have been detected. The remaining 50% would have occurred in those aged less than 35 years. The actual cost of the first trimester screening programme amounted to 29% of the cost that would have been incurred by a second trimester screening programme, and 100% of Trisomy 21 fetuses were diagnosed.

If strict protocols were implemented and CVS was performed in only high risk patient with a risk cut off of 1:300 or more, then the cost incurred would have been only 21% of that which would have applied to a second trimester screening programme.

4. DISCUSSION

During this study period, there were a total of 428 women who received first trimester screening. The racial distribution was normal for a South African population.

4.1 SCREENING CHARACTERISTICS

4.1.1 MATERNAL AGE

The *a priori* risk determined by a maternal age of greater than 34 years, was previously the sole criterion used to delineate women who were at high risk of having a fetus with a congenital abnormality, especially Trisomy 21. It does stand to reason that a women's risk of having an abnormal fetus should not be substantially increased when she is 35 years old in comparison to her risk on the eve of her 35th birthday. The fact that there is no statistical difference between the mean ages of women who screened positive and women, who screened negative (Table 3.1), substantiates this. Hence, whilst maternal age is an important factor in determining the *a priori* risk, it is no longer the sole criterion for screening and all women should receive first trimester screening if possible.

4.1.2 GESTATIONAL AGE

Nuchal translucency varies with gestational age and no single cut-off value can be used to predict aneuploidy, as has already been pointed out. Accordingly, the precise ascertainment of gestational age is important to achieve an accurate nuchal translucency screen. In this study it became apparent that the majority of women were not accurate in their recall of their last normal menstrual period. A first trimester ultrasound examination would thus also promote accurate dating of the pregnancy.

4.1.3 NUCHAL TRANSLUCENCY AND CROWN RUMP LENGTH

The NT measurement usually increases with gestational age.[45] In this study, fetuses that screened positive were more likely to have a nuchal translucency in excess of 2.5mm and were significantly shorter in length than fetuses that screened negative, possibly due to an early onset of intra-uterine growth restriction. In women who cannot recall their last menstrual period correctly, the benefit of early sonographic dating may be negated if there is early onset intra-uterine growth restriction.

4.2 CHORIONIC VILLUS SAMPLING

Of the 59 patients who screened positive, 24 elected to have chorionic villus sampling, and 5 chromosomal abnormalities were detected (2 Trisomy 21, 1 Trisomy13, 2 Trisomy18, 1 Turners syndrome), and 1 single gene defect (Tay-Sach's disease). The patient in whom a fetus with Tay-Sach's disease was diagnosed, had screened positive with a nuchal translucency measurement of 2.8 mm, and although there is no current literature to support the diagnosis of a single gene defect by means of assessment of nuchal translucency, the positive screen may have been related to the genetic defect.

Of the 356 patients who screened negative, 2 had an increase in their adjusted risk when it was compared to their *a priori* risk. When these women received counseling, it was communicated to them that their risk of having a congenitally abnormal fetus was higher than their *a priori* risk had suggested and one of them elected to have chorionic villus sampling when offered. A diagnosis of Trisomy18 was made in that fetus.

The other patient chose to forgo invasive procedural diagnosis in favor of a 20 week follow-up sonographic evaluation and there were no structural abnormalities, nor sonographic markers of aneuploidy, detected.

Whilst the cut of limit for chorionic villus sampling has been set at 1:300[1], it is difficult, when counseling a patient, to reassure the patient that the adjusted risk, though increased is "acceptable".

Respect for autonomy is a central principle in ethics and in law[46]. It is not uncommon for women to decline an invasive procedure even if the risk of aneuploidy is higher after a first trimester screen, and this decision must be respected. By the same token, some women find even a minimal increase in the adjusted risk unacceptable. Hence, the above-mentioned patient with a negative screen but an increase in the adjusted risk opted to have invasive testing performed. Implementation of this principle, led to the detection of one fetal aneuploidy in the group who screened negative, but had an increase in the adjusted risk. An increase in the adjusted risk may be as important as a positive screen of 1:300.

The fetus which falsely screened negative had a karyotype of Trisomy 18, and it is possible that the false negative result was related to the specific abnormality. There have been several reports where it was observed that fetuses with a Trisomy 18 karyotype displayed an early resolution of increased nuchal translucency.[47,48] Celentano, *et al*[47], described an increased nuchal translucency of 2.3mm at 12 weeks gestation, which had resolved to 1.6mm at 14 weeks gestation. The same phenomenon, of early resolution of an increased nuchal

translucency, has been described in Trisomy 13.[48] To address this problem, Celentano, *et al*[47] reinforced the importance of first trimester biochemical screening.

4.2.1 INVASIVE PROCEDURE LOSS RATE

One patient, who had screened negative, but had elected to have chorionic villus sampling for the purpose of paternity testing, had a miscarriage within 24 hours of the procedure. This was the only pregnancy loss attributable to the procedure which occurred in the study. Loss rates, exclusively due to chorionic villus sampling, have been quoted to be between 7.6% and 14 %.[7]

4.2.2 GENDER DISTRIBUTION

Male fetuses were observed to have a greater frequency of false positive screens and male fetuses were more likely to screen positive. This finding suggests that male fetuses may have a larger nuchal translucency measurement than female fetuses. There is no supporting data for these findings and this most certainly merits further investigation. (Table 3.3)

4.3 STRUCTURAL ABNORMALITIES DETECTED

Only one of the three Trisomy 21 fetuses had a structural abnormality detected on anatomical survey. This fetus had the characteristic 'lemon sign' which has frequently been described.[7] The mother of this fetus declined invasive procedural diagnosis, and the presence of the abnormality was confirmed after delivery.

The two fetuses with suspected Trisomy 13 had multiple structural abnormalities. One had holoprosencephaly, cyclopia, an increased nuchal translucency and an exomphalos. On the

grounds of these findings the mother requested a termination of pregnancy and the karyotype was confirmed to be normal after delivery. The other fetus had only an exomphalos and the post CVS karyotype revealed Trisomy of chromosome 13.

Of the two fetuses with multi-structural defects, the one had gastroschisis; renal agenesis and bilateral clubbed feet and the other had kyphoscoliosis, an exomphalos, polydactyly, and bilateral clubbed feet. In view of the severity of the abnormalities, the parents of both fetuses elected to terminate the pregnancies and both the karyotypes were found to be normal post termination.

As observed in Table 3.4, first trimester screening has proven to be valuable in the diagnosis of multi-structural.

4.4 FIRST TRIMESTER SCREENING IN TWIN PREGNANCIES

Table 3.5 demonstrated no significant difference between the mean ages of women with dichorionic twin pregnancies when compared to those with monochorionic twin pregnancies. There were no aneuploid fetuses among the twin pregnancies. The mean nuchal translucency was significantly higher in monochorionic twins. This data is similar to the findings in previous studies.[9] Sebire, *et al*[49] reported a 1.5 times greater nuchal translucency in monochorionic twins compared with dichorionic twins.

4.5 EVALUATION OF FIRST TRIMESTER SCREENING PROGRAM

The Chris Hani Baragwanath hospital first trimester screening programme to detect structural and chromosomal abnormalities was found to have a sensitivity of 92.9% and a specificity of 88.6%. The screening programme therefore has a high positive and negative predictive value.

These results compare favorably with the findings of Snijders, *et al*[1], where they achieved a sensitivity of 82% for a false positive rate of 8.3% when first trimester screening for Trisomy 21 was implemented without biochemical screening. The high false positive rate noted in the Chris Hani Baragwanath Hospital screening programme can probably be attributed to the fact that a population at high risk was selected for screening.

Although this first trimester screening programme is meant to target the general population, patients attending the Chris Hani Baragwanath Hospital are usually referred for antenatal care due to previous poor outcomes and complications experienced in the index pregnancy. This lowered the threshold for invasive testing and the high false positive rate can possibly be attributed to this.

The overall Chorionic villus sampling uptake rate was high because strict criteria for offering the test were not adhered to. However, the Chorionic villus sampling rate of women who actually required the test (women with a risk of 1:300 or more) was 5.7%, which is also in keeping with the findings of Snijders, *et al*.[1] The data obtained reflects that the service offered to patients at the Chris Hani Baragwanath Hospital is effective and is comparable with international standards.

With the ever increasing prevalence of human immunodeficiency virus seropositivity among patients, it is of utmost importance to limit the invasive procedure rate. The employment of first trimester nuchal translucency screening, as opposed to second trimester screening followed by amniocentesis, is one way of achieving such limitation.

Furthermore the first trimester nuchal translucency screening programme at the Chris Hani Baragwanath Hospital has been found to be of value in screening for structural as well as chromosomal abnormalities in a South African population.

4.6 COST EFFECTIVENESS OF THE CHRIS HANI BARAGWANATH HOSPITAL FIRST TRIMESTER SCREENING PROGRAM

Table 3.7 demonstrates that the first trimester screening programme for Trisomy 21 is cost effective in terms of the percentage of Trisomy 21 diagnosed versus the cost which would have been incurred when compared to a second trimester screening programme.

It would be difficult to use the data obtained from this study to evaluate the cost effectiveness with respect to the diagnosis of abnormalities other than Trisomy 21, as there is no data to support the comparison of screen positives and negatives in the first and second trimesters.

In a country like South Africa were budget limitations dictate the quality of medical services provided, the first trimester screening programme has, in this study, been shown to be cost effect with an internationally equivalent efficacy.

4.7 CONCLUSION

This retrospective descriptive analysis of nuchal translucency as a method of first trimester screening for abnormalities has revealed interesting results.

The population screened reflected a South African racial distribution. Only 26% of women were of advanced maternal age and only 1 had a fetus with Trisomy 21. There was no significant difference between the mean ages of women whose fetuses screened positive and those who screened negative.

Fetuses which screened positive had a smaller crown rump length than those who screened negative, and this could possibly be attributed to an early onset of intra-uterine growth restriction.

Chorionic villus sampling results suggest that an increase in the adjusted risk is as important as a screen positive result. The incidental diagnosis of Tay-Sach's disease, though unsubstantiated by a literature review, suggests that this single gene defect may be amenable to early detection by the implementation of first trimester nuchal translucency screening. This would require further investigation in the future. Sub-analysis of gender predisposition suggests that male fetuses have a higher tendency to be affected as well as to falsely screen positive. This finding also requires further investigation in a study with a greater power.

The first trimester screening programme is beneficial in the diagnosis of both structural abnormalities and chromosomal abnormalities, especially the Trisomies. More importantly

this screening programme has a sensitivity of 92.9% at an overall invasive procedure uptake rate of 7.9% which is comparable to international data. The high false positive rate of 11% may be attributed to the screening programme being implemented to a high risk population at a tertiary care institution.

The benefit of a reduced procedure rate in the setting of a high seropositivity of the Human Immunodeficiency Virus would support the implementation of a first trimester screening programme.

The Chris Hani Baragwanath Screening programme has addressed the ever present cost factor and provides effective screening at a third of the cost that would have been incurred if the same patients were screened in the second trimester. The cost and benefit in terms of man-hours required to implement the programme in the general population remains to be assessed.

In order to ensure sustainability and development of this programme, more doctors need to receive the appropriate training and accreditation to perform first trimester nuchal translucency screening. In addition, the public needs to be made aware that such a test exists and more screening centers need to be made available to the public. The bottom line is additional funding.

ILLUSTRATION CREDITS

FIGURE 1-1, 1-2, and 2-2, Reproduced with permission of the editor Prof KH Nicolaides from *The* 11-14 *Week Scan. The Diagnosis of Fetal Abnormalities.* New York: Parthenon Publishing,1999.

FIGURE 1-3, 1-4, 1-5, 1-6, and 2-1, were kindly provided by Prof E Nicolaou, Principal Specialist in Fetal Medicine at the Chris Hani Baragwanath Hospital, from his personal collection of sonographs.

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APPENDIX A

Data capture Sheet

Reference no						
Date of birth						
Age						
Last normal menstrual period						
Period of amenorrhoea						
Estimated date of delivery						
Previous chromosomal abnormality	T13	T18	T13	Other		
Ultrasound findings						
Fetal heart rate						
Crown rump length						
Biparietal diameter						
Nuchal translucency						
Gestational age						
Skull / Brain						
Normal	Not examined	Accrania	Lemon sign	Encephalocoele	Ventriculomegaly	Holo-prosencephaly
Spine						
Normal	Not examined	Spina bifida	Kyphoscoliosis			
Stomach						
Visualized	Not examined	Intrathoracic				
Hands						
Normal	Not examined	L absent	R absent	Both absent		
Abdomen						
Normal	Not examined	Exomphalous	Gastroschisis			
Bladder						
Visualized	Not visualized	Not examined	Megacystis			
Feet						
Normal	Not examined	L absent	R absent	Both absent		
Maternal Biochemistry						
Date	Gestational Age		W D			
Maternal weight	Smoking Y	Caucasian	Afro-carribean	Asian	Oriental	
Free Beta hCG		MOM				
PAPP A		MOM				
Background risk		Adjusted Risk				
Karyotype						
Maternal age	Age related risk	Gender of fetus M F				
Chromosomal abnormalities						
21	18	13	X	Y		
Outcome of pregnancy						
Gestation	Male	Female	Abnormality			
Type of abnormality						

APPENDIX B

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Naidoo

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M041108**
PROJECT	Nucha; Translucency as a Method of First Trimester Screening for Aneuploidy in a South African Population
INVESTIGATORS	Dr P Naidoo
DEPARTMENT	School of Clinical Medicine
DATE CONSIDERED	04.11.26
DECISION OF THE COMMITTEE*	Approved subject to devising a useful data consent

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 04.11.29 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr E Nicolaou

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES