

**Original Communication****PATTERNS OF ORBITOFACIAL AND ORBITAL GROWTH AT PRENATAL STAGE DERIVED FROM FETAL AUTOPSY STUDIES****Tulika Gupta<sup>1\*</sup>, Kanchan Kapoor<sup>2</sup>, Balbir Singh<sup>2</sup>, Anju Huria<sup>3</sup>**<sup>1</sup>*Department of Anatomy, Institute of Dental Sciences and Hospital, Panjab University, Chandigarh, India*<sup>2</sup>*Department of Anatomy, Government Medical College and Hospital, Chandigarh, India*<sup>3</sup>*Department of Obstetrics & Gynecology, Government Medical College and Hospital, Chandigarh, India***RESUMEN**

Objetivo: Las mediciones orbitofaciales y orbitales del feto pueden ser útiles para el diagnóstico precoz prenatal de malformaciones craneofaciales. La mayoría de los estudios anteriores se basan en la ecografía y sólo hay unos cuantos estudios basados en autopsias fetales. El Análisis detallado de los distintos parámetros puede proporcionar una base de datos útil para una rápida referencia. Métodos: En cincuenta fetos normales de edades gestacionales diferentes, se midieron los siguientes parámetros: La distancia cantales externa e interna, la longitud de la hendidura palpebral, la longitud oropalpebral, la profundidad y la anchura de la órbita y la distancia interorbital. Resultados: El análisis estadístico reveló una correlación positiva significativa de todos estos parámetros con la edad gestacional y con el diámetro biparietal. Los patrones de crecimiento de los parámetros orbitales y orbitofacial también demostraron una correlación significativa entre sí. Conclusión: Nuestros resultados muestran que el aumento de las partes laterales de la cara y de la longitud facial vertical se produce a un ritmo más rápido en comparación con la parte media de la cara. Las desviaciones de los datos normativos generados para los parámetros orbitales y orbitofacial ayudarán en la detección precoz de síndromes genéticos específicos.

**Palabras clave:** autopsias fetales, biometría fetal, órbita fetal, crecimiento facial, morfometría.

**ABSTRACT**

Objective: Fetal orbitofacial and orbital measurements may be helpful in early prenatal diagnosis of craniofacial malformation. Most of the earlier studies

are ultrasound based and there are only a few studies based on fetal autopsies. Comprehensive analysis of various parameters can provide useful database for easy reference. Methods: In fifty normal fetuses of different gestational ages, the following parameters were measured: outer and inner canthal distances, palpebral fissure length, oropalpebral length, depth and width of orbit and inter orbital distance. Results: Statistical analysis revealed significant positive correlation of all these parameters with gestational age and biparietal diameter. The growth patterns of the orbitofacial and orbital measurements also demonstrated significant correlation between these parameters. Conclusion: Our results demonstrate that the lateral parts of the face and the vertical facial length grow at a faster rate than the median part of the face. Deviations from the normative data generated for the orbitofacial and orbital parameters will help in early detection of specific genetic syndromes.

**Key words:** fetal autopsy; fetal biometry; fetal orbit; facial growth; morphometry.

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## INTRODUCTION

The study of fetal growth and development by prenatal ultrasound has been facilitated by the availability of anthropometric standards for the fetal body (Escobar et al., 1988). Fetal biometry could be a valuable tool in syndrome delineation and also for distinguishing normal and abnormal craniofacial development (Roelfsema et al., 2007). Such data will not only contribute to a description of facial dysmorphogenesis but will also lead to a better understanding of normal facial growth and development. Craniofacial measurements may prove to be an useful tool for prenatal diagnosis and gestational aging (Escobar et al., 1988).

Various craniofacial and orbital fetal measurements at different gestational ages have been described. (Burdi et al., 1988; Denis et al., 1998; Diewert, 1985; Escobar et al., 1988; Escobar et al., 1990; Guihard-costa et al., 2003; Guihard-costa et al., 2006; Kragsskov et al., 1997; Roelfsema et al., 2007; Sibert, 1986; Sivan et al., 1997; Wu et al., 2000). Most of these studies are ultrasound based and there are only a few reports based on fetal autopsies. A comprehensive statistical analysis of various facial and orbital parameters is not widely reported. It is desirable that local values derived from well defined population groups be used as a reference in the evaluation of fetuses with dysmorphic facial features in order to avoid errors in diagnosis due to racial variations. (Adeyemo et al., 1998).

The present study was designed to generate morphometric data for specific facial and orbital parameters across various gestational ages in fetuses of North-West Indian population.

## MATERIALS AND METHODS

The present study was conducted from July 2008 to November 2009, on fifty normal fetuses received by Department of Anatomy, Government Medical College and Hospital, Chandigarh after ethical clearance from the college ethical committee. The fetuses were from therapeutic and spontaneous abortions. They were preserved in 4% formaldehyde solution right after delivery. Fetuses which were diagnosed with intra-uterine growth retardation (IUGR) and malformed fetuses with cranio-facial or ocular abnormalities, chromosomal disorders, or neurological defects that could affect cranial or orbitofacial growth, were excluded from the study.

Fifty fetuses, 23 males and 27 females were included in the study. Gestational age was determined based on the last menstrual period which was confirmed by the first trimester and/or the early second trimester ultrasound examination. Fetuses were divided into 18 groups according to the gestational age (in weeks), ranging from the 11<sup>th</sup> to the 36<sup>th</sup> week of intrauterine life with no representation for the 13<sup>th</sup>, 15<sup>th</sup>, 25<sup>th</sup>, 30<sup>th</sup>, 31<sup>st</sup>, 33<sup>rd</sup> and 35<sup>th</sup> weeks of intrauterine life. Each group contained fetuses from a single gestational week. Measurements were done with the help of sliding vernier calipers with an estimated precision of .02 mm. Parameters were measured twice and the mean of both values was used. All the measurements were done by a single person and were recorded in centimeters (except fetal age). Following parameters were studied:

- A. Anthropometric measurements:
  1. Gestational age in weeks
  2. Crown heel length (height)
  3. Biparietal diameter (BPD)
  4. Weight in gm, (measured before processing of the fetus)
- B. Orbitofacial parameters:
  5. Outer canthal distance (OCD): The distance between the outer canthi of right and left eye.
  6. Inner canthal distance (ICD): The distance between the inner canthi of right and left eye.
  7. Palbebral fissure length (PFL): The distance between the outer canthus and the inner canthus of each eye.
  8. Oropalpebral length (OPL): The distance between the outer canthus of the eye and the angle of the mouth on the same side.
- C. Orbital measurements:
  9. Depth of the orbit (DO): The distance between the centre of the orbit (at the level of the orbital rim) and apex of the orbit.
  10. Width of the orbit (WO): The maximum transverse distance measured between the right and the left margin of an orbit.
  11. Inter orbital distance (IOD): The transverse distance between the centers of the two orbits, measured at the level of the orbital rim.

Anthropometric and orbitofacial parameters were noted first. The orbital measurements were taken after the eye balls were removed from the orbits.

Age (n)	BPD	OCD	ICD	IOD	PFL	OPL	DO	WO
11 (1)	.70	.72	.28		.19	.30		
12 (1)	1.39	1.10	.49	.81	.48	.59	.41	.35
14 (3)	2.04±.37	1.5±.27	.69±.18	1.0±.00	.59±.12	.86±.09	.70±.10	.59±.03
16 (2)	2.4±1.12	1.77±.76	.60±.14	.97±.5	.7±.28	.98±.36	.78±.25	.70±.28
17 (2)	3.15±.5	2.5±.42	.95±.21	1.66±.34	.90±.14	1.22±.18	1.25±.00	.95±.07
18 (9)	5.05±3.52	3.03±.22	1.0±.12	1.91±.19	1.06±.10	1.57±.16	1.16±.23	1.08±.34
19 (6)	3.74±.84	3.18±.92	.99±.15	1.80±.48	1.07±.18	1.65±.16	1.30±.57	.87±.13
20 (5)	3.90±.69	2.82±.55	1.13±.40	1.56±.50	1.02±.11	1.56±.23	.97±.20	.90±.13
21 (4)	4.58±.3	3.33±.14	1.20±.08	1.92±.66	1.16±.11	1.44±.62	1.54±.33	1.14±.19
22 (1)	4.30	3.44	1.20	1.75	1.17	1.85	1.65	1.90
23 (4)	5.20±.72	4.04±.32	1.50±.08	2.60±.19	1.40±.18	2.17±.19	1.67±.29	1.10±.11
24 (4)	5.16±.35	3.92±.32	1.46±.28		1.52±.16	2.19±.21	1.87±.14	1.24±.08
26 (2)	6.15±.21	4.30±.00	1.41±.15	2.53±.12	1.52±.06	2.75±.01	1.98±.44	1.39±.15
27 (1)		3.48	1.38		1.05	2.10	2.10	1.30
28 (2)	4.14±.90	3.01±.79	1.09±.29	1.70±.70	1.08±.16	1.62±.53	1.27±.41	.81±.04
29 (1)	5.32	3.73	1.38	2.60	1.33	2.00	1.58	1.150
32 (1)	5.00	3.90	.90	2.50	1.40	2.32	1.47	1.00
36 (1)	8.50	5.78	1.93	3.18	1.36	3.40	1.79	1.42

**Table 1:** Mean values of the orbital, orbitofacial and anthropometric data. Age-gestational age in weeks, n-number of fetuses Wt-weight in gm, Ht-height in cm., BPD-biparietal diameter in cm, OCD-outer canthal distance in cm, ICD-inner canthal distance in cm, IOD-interorbital distance in cm, PFL-palpebral fissure length in cm, OPL-oropalpebral length in cm, DO-depth of orbit in cm, WO-width of orbit in cm.

The depth of the orbit was measured at the centre of the orbit. The Width of the orbit was taken at the rim of the orbit. The inter-orbital distance (the distance between the centers of the right and the left orbits) was also measured at the level of the orbital rim.

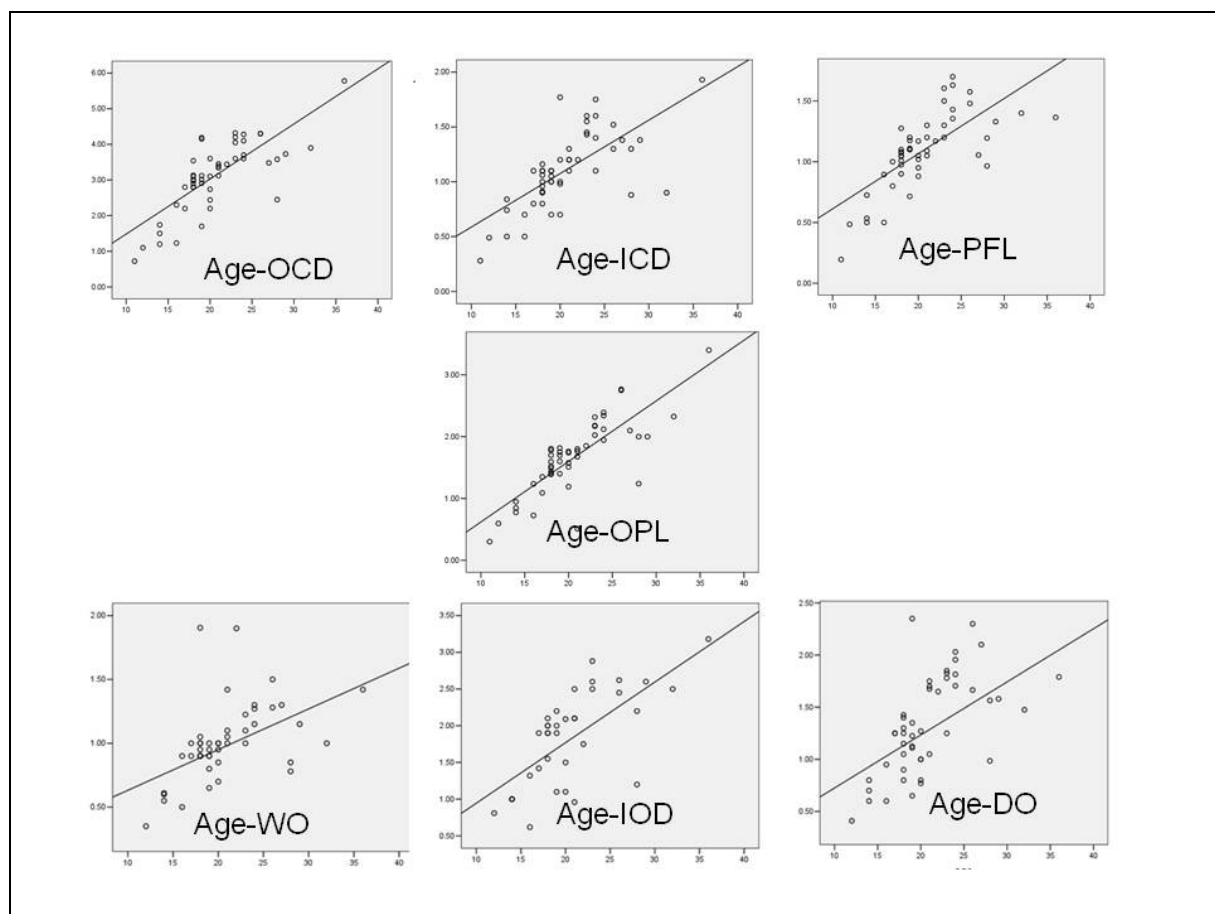
Data was grouped into anthropometric, orbitofacial and orbital groups. Correlations were tested among all parameters by Spearman rank correlation. The growth pattern of orbitofacial and orbital parameters was studied by adjusted  $r^2$  values.

**RESULTS**

A total of 50 fetuses were studied out of which 27 were females. There was a significant correlation

between increase in the gestational age and the increase in weight and BPD. BPD was found to have maximum correlation with age ( $p=.000$ ). The height and weight did not correlate significantly with BPD. Therefore in further analysis age and BPD were the parameters against which various orbital and ocular parameters were compared.

The mean values of orbitofacial and orbital parameters on the right and the left side were calculated for each gestational age group. A paired sample correlation test with 95% confidence interval did not demonstrate a significant difference in any of these parameters between the right and the left sides. For further analysis of the results the combined means of the right and left values was used. Gender wise analysis was also done. Means of all studied parameters are given in Table 1.

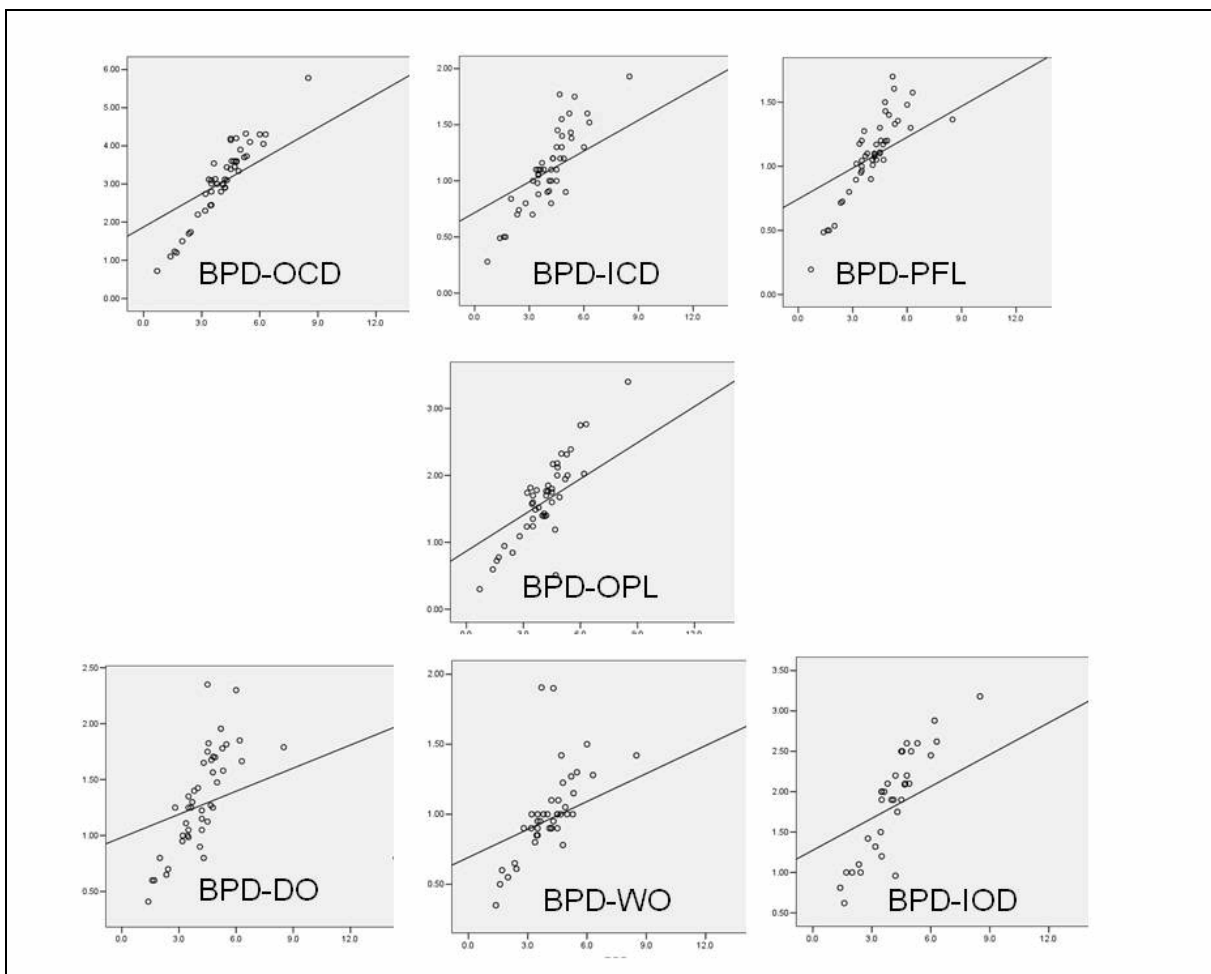


**Figure 1-** Relationships of gestational age with outer canthal distance (OCD), inner canthal distance (ICD), palpebral fissure length (PFL), oropalpebral length (OPL), orbital depth (DO), orbital width (WO) and interorbital distance (IOD). The X axis represents the gestational age (in weeks) in all figures and Y axis represents the values for OCD, ICD, PFL, OPL, DO, WO and IOD clockwise as shown.

**Orbitofacial parameters**

For statistical analysis, Spearman rank correlation was used. There was a significant correlation between increase in gestational age and all the orbitofacial (OCD, ICD, PFL & OPL) parameters ( $r=.716-.794$ ,  $p=.000$ ) (Figure 1). Similar significant positive correlation was observed between BPD and all orbitofacial measurements ( $r=.785-.858$ ,  $p=.000$ ) (Figure 2). These four orbitofacial parameters also demonstrated significant correlation when

compared with each other, in their growth pattern ( $r=.717-.920$ ,  $p=.000$ ). Gender wise, among male fetuses similar significant correlations were observed when the increase in gestational age and BPD were plotted against OCD, ICD, PFL and OPL. In females, gestational age correlated well with these orbitofacial parameters with significant p values ( $p<.01$ ), but no significant correlation was observed between BPD and all the four orbitofacial parameters ( $r=.288 - .387$ ,  $p>.05$ ).



**Figure 2-** Relationships of biparietal diameter (BPD) with outer canthal distance (OCD), inner canthal distance (ICD), palpebral fissure length (PFL), oropalpebral length (OPL), orbital depth (DO), orbital width (WO) and interorbital distance (IOD). The X axis represents the biparietal diameter (BPD) in all figures and Y axis represents the values for OCD, ICD, PFL, OPL, DO, WO and IOD clockwise as shown.

**Orbital parameters**

Again, using Spearman rank correlation with age as an independent variable, the increase in the depth of orbit (DO), width of orbit (WO) and the inter orbital distance (IOD) were correlated with

the increase in gestational age (Figure 1). There was significant correlation between age and all the three orbital parameters ( $r= 0.594-0.711$ ,  $p=.001$ ). The increase in the DO, WO and IOD also correlated well ( $r=0.694-0.802$ ,  $p=.000$ ).

Similarly significant correlation was found between the increase in BPD and the corresponding increase in DO, WO and IOD ( $r=0.743-0.812$ ,  $p=.000$ ). (Figure 2).

All these orbital parameters were tabulated separately for males and females. Correlation was calculated in both sexes separately. Among males there was a good correlation between all the orbital parameters with age and BPD. In females, increase in the gestational age correlated significantly with DO ( $r=0.587$ ,  $p<.002$ ) and to some extent with IOD ( $r=0.501$ ,  $p<.024$ ) but there was no statistically significant correlation with WO ( $r=0.267$ ,  $p<.197$ ). When the growth of the BPD was plotted against the orbital

parameters in the females no statistically significant correlation was found ( $r=0.170 - 0.307$ ,  $p>.01$ ). However the three orbital parameters correlated well among themselves ( $r=0.664 - 0.842$ ,  $p<.000$ ).

The quantum of increase in different parameters with each gestational week was statistically analyzed to observe the differential growth for each parameter, denoted by  $r^2$  and adjusted  $r^2$  (Table 2). The  $r^2$  changes for OCD were relatively greater than the  $r^2$  changes for ICD and IOD. The parameters PFL and OPL also demonstrated greater  $r^2$  change with increase in each gestational week as compared to IOD and ICD.

Index*	Change Statistics					
	R Square Change	Adjusted R Square Change	F Change	df1	df2	Sig. F Change
BPD	.258	.241	15.609	1	45	.000
OCD	.587	.579	68.299	1	48	.000
ICD	.473	.462	43.107	1	48	.000
IOD	.467	.452	29.842	1	34	.000
PFL	.508	.498	49.564	1	48	.000
OPL	.642	.635	84.465	1	47	.000
DO	.375	.362	27.623	1	46	.000
WO	.238	.221	13.746	1	44	.001

**Table 2-** Table depicting the quantum of increase in each parameter with unit increase in gestational age (per week). \*BPD-biparietal diameter, OCD-outer canthal distance, ICD-inner canthal distance, IOD-interorbital distance, PFL-palpebral fissure length, OPL-oropalpebral length, DO-depth of orbit, WO-width of orbit.

## DISCUSSION

In recent years enormous progress has been made in the understanding of normal prenatal craniofacial development. Molecular genetics and animal models for studying the role of genetic and environmental factors relevant to fetal malformations have provided insights into abnormal development. (Jhonston and Bronsky, 1995). Parallel to the understanding of genetics and cell migration, there are studies involved in determining growth of fetal facial and orbital structures and their correlation with the corresponding development of the skull (Denis et al., 1998).

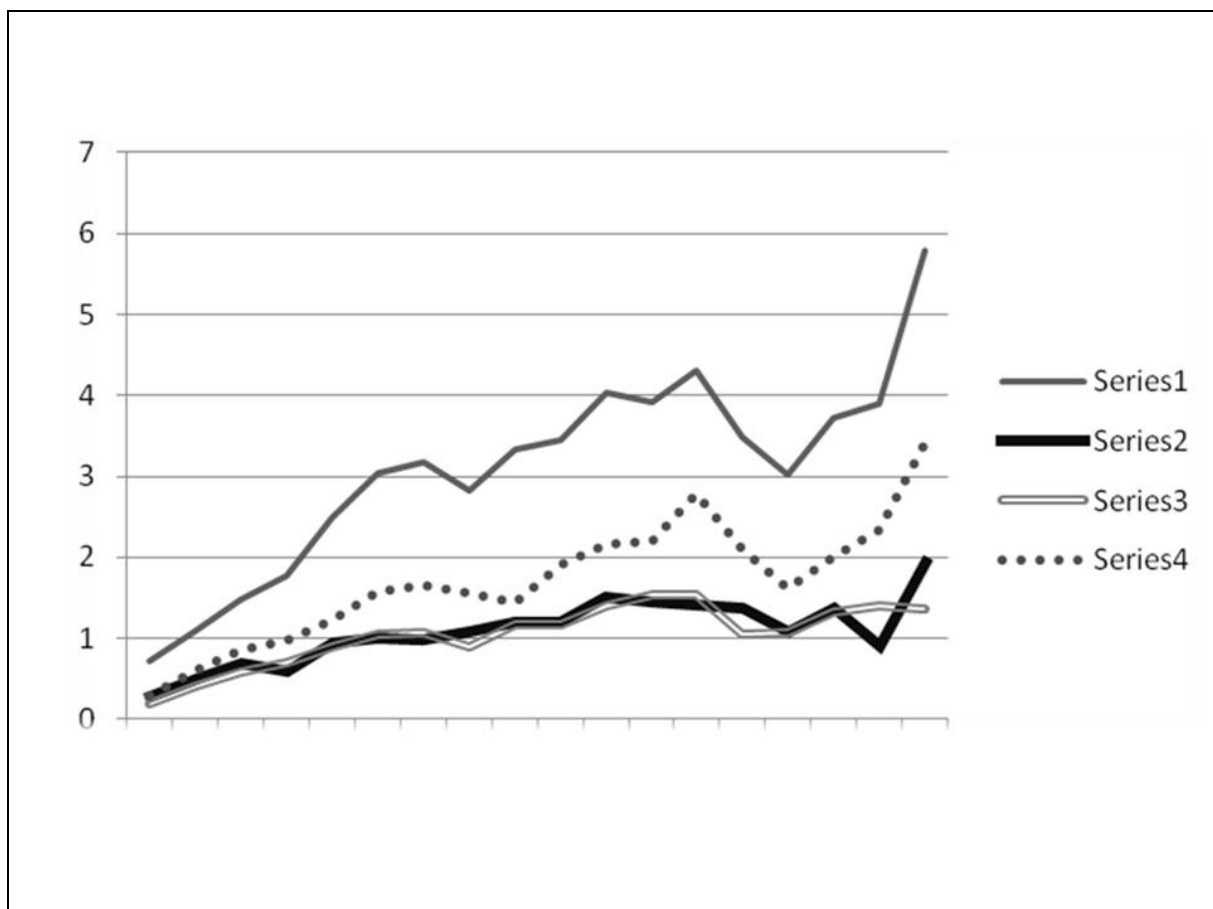
Early diagnosis of craniofacial dysmorphic syndromes is directly linked to availability of normative fetal biometric data. As there can be significant racial and ethnic variations, data derived from one population group cannot be extrapolated for establishing deviations from normal fetal measurements in a different population group. The present study has generated morphometric fetal data for various orbitofacial and orbital parameters in North-West Indian population.

In the present study, the orbital as well as orbitofacial growth parameters were determined

at different gestational ages (11<sup>th</sup> – 36<sup>th</sup> week). All the parameters had a significant and positive correlation with increase in gestational age and BPD. In addition to age and BPD, orbital and orbitofacial values correlated significantly with each other. The mean values for these parameters at different gestational ages were derived. These would be useful in developing growth charts for the population against which deviation from the normal fetal parameters could be studied. Measurement of orbital and orbitofacial values during routine antenatal ultrasound would thus be extremely useful in diagnosis of craniofacial malformation syndromes and possibly, in future, in utero fetal therapeutic interventions.

Different orbital and facial parameters have been measured in utero by antenatal ultrasound. (Escobar et al., 1990; Sivan et al., 1997; Roelfsema et al, 2007) The exact parameters as well as the gestational ages studied vary in

different reports. Thus it is not practical to compare absolute fetal measurements from the present study with other ultrasound based studies. In a biometric study of human fetuses from France, a wide range of gestational ages were included, as in the present study. At gestational age 18.5-20 weeks, the OCD, ICD, PFL and OPL were 3.15 cm, 1.27 cm, 0.9 cm and 1.8 cm respectively while in the age group of 25.5-28 weeks values were 4.3 cm, 1.63 cm, 1.34 cm and 2.5 cm. These values are close to the measurements in the present study at approximately similar gestational ages (Table 1). Although the French study does not mention the racial or ethnic sub grouping of the fetuses, our population would be expected to be different. Thus, it is necessary to have region based and population based data across similar gestational ages and measuring the same set of fetal parameters for any meaningful comparison.



**Figure 3-** Relative growth of lateral face (series 1: outer canthal distance & series 4: oropalpebral length) as compared to the median face (series 2: inner canthal distance & series 3: palpebral fissure length). The X axis represents gestational age in weeks.

The adjusted  $r^2$  models probably best describe the growth of each parameter. Quantitative growth of each parameter per unit change in gestational age (week wise) was also studied by the regression model and the  $r^2$  changes were calculated. The  $r^2$  changes were more in PFL, OCD and OPL as compared to ICD and IOD. These results demonstrate that the lateral parts of the face (outer canthal distance) as well as vertical facial length (oro-palpebral length) increase at a faster rate as compared to growth of median parts of the face (inner canthal distance and inter-orbital distance) (Fig. 3). Denis et al (1998) asserted that the growth of the skull predominates over that of the face and that the face grows more rapidly along its vertical axis than along its horizontal axis. Vertical growth of the face more closely follows that of the skull as compared to the horizontal growth. Measurement of relative growth rates of the fetal skull and face from numbered contours of photographs and roentgenograms of the head were analyzed by Trenouth (1991). Facial length growth rate was more than that of width. Siebert (1986) also stated that the centre of the face seems to grow slower than the sides of the face and concluded that the transverse growth is probably more rigidly controlled than the sagittal growth. These findings have been corroborated in our study as well. The present study has resulted in generating data about fetal orbitofacial and orbital growth patterns in North-West Indian population. Further work including larger number of fetuses in different gestational ages is desirable to have a higher predictive value.

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