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Reference Intervals for the ratio of Soluble FMS-like Tyrosine Kinase-1 and Placental Growth Factor in Pregnant and Non-Pregnant Females in Pakistani Population

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ABSTRACT

Introduction: To derive the reference intervals of serum soluble FMS like tyrosine kinase -1/Placental growth factor ratio in pregnant and non-pregnant females.

Aims & Objectives: To derive the reference intervals of serum soluble FMS like tyrosine kinase -1/Placental growth factor ratio in pregnant and non-pregnant females.

Place and Duration of Study: A comparative Cross-sectional study conducted in department of Chemical Pathology and Immunology, Chughtai Institute of Pathology, Lahore from February 2024 till May 2024

Material & Method: Blood samples from 120 pregnant and 120 non-pregnant females from 14±1 to 27±1 weeks were taken. All participants were of reproductive age group, disease free, non-hypertensive, non-diabetic, without any inherited or autoimmune disorders and not any significant drug history. Levels of placental growth factor (PGF) and soluble FMS like tyrosine kinase -1(sFlt-1) were estimated by Elecsys cobas e601. Data was analysed by SPSS 21. Shapiro-Wilk test and Kolmogorov Smirnov test were applied. p value <0.05 revealed that data findings were non-Gaussian. Reference intervals were calculated by rank-based method.

Results: The reference intervals of serum sFlt-1/PGF ratio in non-pregnant females were 5.36 to 18.40 and in pregnant females 0.61 to 24.45 and they were determined on 2.5th and 97.5th centiles using 90% confidence interval.

Conclusion: sFlt-1/PGF ratio can act as a predictive biomarker for cardiovascular disease in non-pregnant females and for pre-eclampsia in pregnant females. Current study findings would be helpful for healthcare providers to identify high-risk groups. The identification of low-risk groups results in a shorter duration of hospitalizations with potential economic benefits.

Keywords: Reference intervals, sFlt-1/PGF ratio, pre-eclampsia, rank based method

INTRODUCTION

According to the Global Health Organization, worldwide the incidence of preeclampsia varies between 2% to 9% of pregnancies. 1.7% to 16.8% of pre-eclampsia cases are reported in developing countries, while the rate of pre-eclampsia in developed countries is about 0.4%.[1,2] The definite pathogenesis of pre-eclampsia is still unclear but the angiogenic imbalance began as an essential mechanism to understand the complexity of placenta-related disorders, which include intrauterine growth retardation, recurrent spontaneous abortion, pre-eclampsia, and eclampsia.[3] Placental growth factor (PGF) is a multi-functional cytokine produced by various cell types, including the placental trophoblastic cells. As a family member of vascular endothelial growth factor (VEGF), PGF acts synergistically with VEGF that is required for the preservation of endothelial cell well-being during pregnancy.[4] The biological interest of PGF is regulated through a soluble portion of the FMS-like tyrosine kinase-1 receptors (sFlt-1), who act as endogenous inhibitor of PGF. In hypoxic placenta there is up regulation of genes encoding for sFlt-1 in trophoblastic cells leading to excessive production of sFlt-1. sFlt-1 binds to PGF with high tendency thereby neutralizing PGF and decreasing its concentration in maternal blood leading to endothelial damage, hypertension and proteinuria around 20 weeks of gestation.[5]

The ratio of these anti-angiogenic and angiogenic proteins i-e., sFlt-1/PGF ratio has been widely valued

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in literature as a predictive and diagnostic biochemical marker for pre-eclampsia. The ratio believed to allow more effective prediction of pre-eclampsia than the individual factor assays alone. The sFlt-1/PGF ratio can identify pregnant females at high risk of pre-eclampsia one to four weeks earlier than onset warning symptoms and signs of pre-eclampsia [6,7,8] while in non-pregnant females sFlt-1 and PGF are expressed in smooth muscles, monocytes, vascular endothelial cells, osteoblasts, fibroblasts. Increase ratio of sflt-1/PGF represents the pathological angiogenesis as well as associated with diabetes mellitus and cardiovascular diseases.[9]

In medical diagnostics, reference intervals are essential tool in quantitative laboratory tests to distinguish between the diseased or disease-free individuals. Reference intervals (RIs) are defined as a set of numerical values determined from the cohort of the reference population obtained from the distribution of the results in them. 95% of disease-free participants test results fall between 2.5th and 97.5th percentile. It has been established by means of logically valid statistical rules and methods[10]. Without reference intervals laboratory investigations would be of little value in clinical practice except for few laboratory parameters where clinical decision limits are available. According to protocols of Clinical and Laboratory Standards Institute, it is essential for diagnostic laboratories to establish their RIs carefully according to standard protocols taking in account the biological variability in reference population. Comparison of patient results with reference intervals is currently the major approach to the clinical interpretation of laboratory data[11,12].

As per author's knowledge RIs of sFlt-1/PGF ratio has not been established in the local Pakistani community. The current study was carried out with the objective to determine the reference intervals of sflt-1/PGF ratio in pregnant and non-pregnant disease-free reference individuals. Higher ratio outside the established reference intervals will help health care providers to identify the pregnant females at high risk of pre-eclampsia and non-pregnant females at risk of cardiovascular diseases. Moreover, this emerging biochemical marker can be cost saving by optimizing surveillance in patients at low risk.

The study aims to determine the reference intervals of the ratio of serum soluble FMS like tyrosine kinase -1 and placental growth factor in pregnant and non-pregnant females.

MATERIAL AND METHODS

A comparative cross-sectional study executed at Department of Chemical Pathology and Immunology, Chughtai Institute of Pathology (CIP) Lahore, Pakistan, carried out from February 2024 till May 2024 after receiving approval from the Institutional Review Board of CIP Lahore (IRB No. CIP/IRB/1239) dated 13-03-2024. 120 healthy non-pregnant females and 120 healthy pregnant females were inducted by non-probability convenient sampling technique. Non-pregnant females were recruited from Chughtai Institute of Pathology phlebotomy reception, females who came with the request of routine health checkup laboratory investigation.

Pregnant females with singleton fetus attending antenatal clinic in Shaikh Zayed Medical Complex Lahore were included from gestational age of 15 to 28 weeks without any known risk factor. Health screening questionnaire was administered to non-pregnant and pregnant females before sample collection to collect demographic information and contact details of the study participants and to exclude the presence of known medical disorders such as diabetes mellitus, pre-existing hypertension, inherited disorders, autoimmune disorders, and significant drug history in them. Written informed consent was obtained from all eligible women of age between 18-45years. Females with any acute or chronic illness, and in menopausal age group were excluded. Pregnant females with multiple pregnancy and diagnosed cases with pregnancy induced hypertension were also excluded. Moreover, hemolytic, icteric and lipemic samples were rejected. From each reference individual 2cc of venous blood was taken to acquire 1cc of serum after centrifugation. Serum become separated and aliquots have been filled and saved at –70°C till subsequent use. Stored samples were thawed before analysis. Physiological and pathological controls were run before sample analysis. Assay PGF and sFlt-1 was estimated through the Elecsys system on a completely automated immunoassay analyzer (Cobas e601) primarily based at the electro-chemiluminescence immunoassay technique. The assay of PGF and sFlt-1 was performed as per manufacturer instruction. Data was analyzed by software SPSS 21. To access the normality of data Kolmogorov-Smirnov test and Shapiro-Wilk test was applied. P- value <0.05 denotes that data distribution was non-Gaussian. Reference intervals of sFlt-1/PGF ratio at 2.5th and 97.5th percentiles at 90% confidence interval (level of significance 0.10) were calculated by Rank based method.

RESULTS

Out of total 240, 120 blood samples have been taken from pregnant women and 120 blood samples from non-pregnant women of reproductive age group (Fig1). Descriptive statistics of Participants are mentioned in (Table 1). The authors decided to go for conventional, direct method (Rank based method)[13] for determination of reference intervals in both pregnant & non-pregnant females as this is a recommended method for International Federation of Clinical Chemistry and Clinical Laboratory Standards Institute for determination of reference intervals.[10,11] For every sample the levels of serum sFlt-1 and PGF were determined in parallel and sFlt-1/PGF ratio was calculated in SPSS. sFlt-1/PGF ratio values were organized in ascending order and rank numbers were assigned. RIs of serum sFlt-1/PGF ratio in non-pregnant and pregnant females were derived on the basis of 2.5th and 97.5th centiles was 5.36 to 18.40 (Table 2) and 0.61 to 24.45(Table 3) at 90% confidence interval while percentile wise reference values of serum sFlt-1/PGF ratio in pregnant and non-pregnant females mentioned(Table 4).

Fig 1: Age Distribution of healthy non-pregnant and pregnant females.

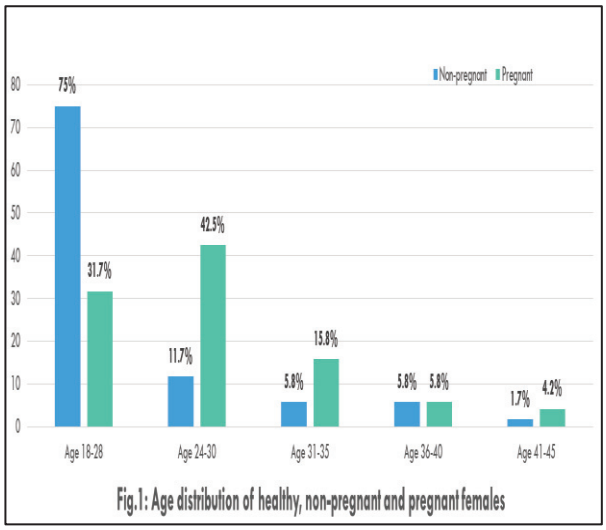

Fig.1: Age distribution of healthy, non-pregnant and pregnant females

Table 1: Descriptive Statistics of Participants with and without pregnancy

Count	Mean	Median	Standard Deviation	Interquartile range	Minimum	maximum
120 (Non-Pregnant females)	10.88	10.36	3.48	4.73	4.42	19.94
120(Pregnant females)	7.05	5.28	6.28	6.28	0.51	28.80

Table2: Determination of RIs of serum sFlt-1/PGF ratio in non-pregnant females by Rank based method

Assigning of rank numbers centiles wise
Lower : 0.025x120+1 = 3.02
Upper : 0.975x120+1 = 117.9
Designating the reference values according to these rank numbers
Lower reference Limit : 2.5th centile 5.36
Upper reference Limit : 97.5th centile 18.40
Calculation of reference values at 90% Confidence Interval
At rank No (R1& R7)
Confidence limit 4.42 & 5.67
Calculation of reference values at 90% Confidence Interval
At rank no: 120+1 = 121-7=114
At rank no: 120+1= 121-1=120
Confidence limit 16.96 & 19.28
Summary
sFlt-1/PGF ratio Lower Reference Limit: 5.36(4.42 to 5.67)
sFlt-1/PGF ratio Upper Reference Limit: 18.40(16.96 to 19.28)

Table 3: Determination of RIs of serum sFlt-1/PGF ratio in the pregnant females by Rank based method

Assigning rank numbers according to centiles
Lower: 0.025x120+1 = 3.02
Upper: 0.975x 120+1 = 117.9
Designating the reference value according to these rank numbers
Lower reference Limit:2.5th centile 0.61
Upper reference Limit: 97.5th centile 24.45
Calculation of reference values at 90% Confidence Interval
Rank No (R1 & R7)
Confidence limit: 0.51 & 0.90
Calculation of reference values at 90% Confidence Interval
At rank no: 120+1=121-7=114
At rank no: 120+1=121-1=120
Confidence limit: 22.07 & 28.80
Summary
sFlt-1/PGF ratio Lower Reference Limit: 0.61(0.51to 0.90)
sFlt-1/PGF ratio Upper Reference Limit: 24.45 (22.07 to 28.80)

Table 4: Percentile-wise reference values of serum sFlt-1/PGF ratio[1]

Centiles	sFlt-1/PGF ratio pregnant females 14±1to 27±1	sFlt-1/PGF ratio in non-pregnant females
5th Centile	0.86	5.65
50th Centile	5.28	10.36
95th Centile	22.60	17.53

DISCUSSION

For clinical laboratories, establishment of reference intervals are essential task. In the current study author determined the reference intervals in statistical language in centiles of the probability distribution of sFlt-1/PGF ratio in the pregnant and non-pregnant disease free female cohorts. High ratio of sFlt-1/PGF is an emerging predictive biomarker for development of pre-eclampsia in the pregnant females and of cardiovascular diseases in non-pregnant females.[17] Worldwide different guide lines recommended the measurement of maternal sFlt-1/PGF ratio as a screening tool to predict development of Pre-eclampsia[18] but inadequate data is available on determination of the RIs of serum sFlt-1/PGF ratio in Pakistani population.

Schoofs et al also reported that high sFlt-1/PGF ratio four weeks before the commencement of severe clinical features of pre-eclampsia in about 82% of high-risk pregnant females whereas the sFlt-1 levels were increased only in half of high risk pregnant females simultaneously. Hence, the sFlt-1/PGF ratio can be better biochemical marker for the prediction of the future development of pre-eclampsia. Present study further elaborates that although individual biomarkers sflt-1 and PGF have been shown to predict pre-eclampsia, but the use of combinations of these biomarkers as sFlt-1/PGF ratio with or without other clinical measurements is the better determinant of the clinical problem and outcome.[19] Vohler et al conducted a case-control, multi-centered study in which they recruited a total of 1149 pregnant females. In the 1st phase they reported reference values of serum sFlt-1, PGF and sFlt-1/PGF ratio in percentiles established on investigating a total of 877 normotensive pregnant females with no pregnancy related risk factors. They suggested the reference values of sFlt-1/PGF ratio from gestational age 24-28 weeks at 5th percentile 0.94, 4.92 at 50th percentile from gestational age 20-23 weeks and 25.7 at 95th percentile from gestational age 15 to 19 weeks.[15] A comparison of 5th, 50th and 95th percentile results corresponds to the percentiles derived in current study. Low values of sFlt-1/PGF ratio in early second trimester is due to low levels of sFlt-1 as compared to PGF, as levels of sflt-1 are stable in the 1st and 2nd trimester then rise gradually till the end of third trimester, while the levels of PGF begins to rise in the first and second trimester and decline at term. (Table V)

Mitlid-Mork B et al investigated 146 pregnant females in a cross-sectional retrospective study from 36±1 to 39±1 week with normal pregnancy outcome. They mentioned sFlt-1/PGF ratio at 5th centile 3.2, at 50th centile 21.3, 110.5 at 95th centile.[16] The results they reported also provide comparison of sFlt-1/PGF ratio in second and third trimester as sFlt-1/PGF ratio increases in third trimester. (Table 5)

A prospective cohort study carried out by Huges et al in a high-risk pregnant females with single alive fetus from gestational age 20 –37 weeks, they established the cut-off value of 38 sFlt-1/PGF ratio to rule out preeclampsia for one week with negative predictive value of 96.2% and ruled in preeclampsia for four weeks with positive predictive value of 75.0%. sFlt-1/PGF >38 was also associated with greater perinatal mortality and morbidity. [20]These findings also support current research finding in a way that in current study sFlt-1/PGF ratio at 95th percentile is 24.0 in healthy pregnant females which is less than the cut off value of 38.0 calculated in high risk pregnant females. Women with suggestive sign and symptoms are frequently hospitalized until placenta related disorders and related adverse consequences have been excluded. Others who require hospitalization may be overlooked. Clinical trials suggests that early detection and monitoring with easily available biomarker would be beneficial.[21] There is a need for a reliable predictive biomarker for pre-eclampsia particularly in its absence in pregnant females. Normal sFlt-1/PGF ratio protect the patient from unnecessary hospital admissions, surveillance and medical interventions, whereas high sFlt-1/PGF ratio justify the provision of cautious maternal monitoring and medication with acetylsalicylic acid (low dose) in high risk group[22]. Concerning about fetal care high tiers of maternal serum sFlt-1/PGF ratio needs timely and optimal management with corticosteroids for fetal lung maturity and provision of intensive care neonatal monitoring [23,24]. Current study findings would be helpful for health care providers to identify high risk group. Identification of low risk group results in shorter duration of hospitalizations, with potential economic benefits.

Limitation: Reference interval studies should be carried out in diagnosed cases of placental disorders important one is pre-eclampsia and eclampsia to determine the cut-off values in diseased females. Present study has one more limitations that reference intervals of sFlt-1/PGF ratio were determined with the use of the Elecsys immunoassays, the results may suffer from inter-laboratory variability due to the different reagent instrument used.

CONCLUSION

This study determined the reference intervals of sFlt-1/PGF ratio in non-pregnant females as 5.36 to 18.40 and in pregnant females 0.61 to 24.45 corresponds to 2.5th and 97.5th centiles. Sflt-1/PGF ratio act as a predictive biomarker for cardiovascular disease in non-pregnant females and of pre-eclampsia in pregnant females for our local population. Recommendations: Besides recommending the integration of sFlt-1/PGF ratio as a routine ante-natal investigation, author also advocated sFlt-1/PGF ratio as an essential screening lab investigation which should be integrated into primary medical centers. The associated threats of early onset pre-eclampsia and iatrogenic pre-term deliveries in high risk pregnant women with high sFlt-1/PGF ratio should refer to developed health care centers timely.

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