

Correlation between Maternal Serum Vascular Endothelial Growth Factor Levels and Fetal Outcome in Females with Recurrent Abortions

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Abstract

Objective: The objective of the study was to analyze the relationship between the maternal serum vascular endothelial growth factor (VEGF) levels and the fetal outcome.

Materials and Methods: It is a comparative study to find the correlation between maternal serum VEGF levels and fetal outcome was evaluated in North Indian women comprising 60 pregnant females with a history of recurrent abortion (study group) and 60 normal pregnant females. The serum VEGF levels of all the females were measured and the correlation of serum VEGF levels and fetal outcome in the form of birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, term/preterm, and intrauterine growth restriction was conducted.

Results: The mean maternal serum VEGF levels in the study group – adverse outcome, study group – normal outcome, and control group – the normal outcome are 486 pg/ml, 546 pg/ml, and 1524 pg/ml, respectively, and there is a positive correlation between serum VEGF and fetal outcome.

Conclusion: The study concluded that there is a positive correlation between the maternal serum VEGF levels and a fetal outcome such as the birth weight, APGAR score, and growth.

Key words: APGAR score, Birth weight, Recurrent abortion, Vascular endothelial growth factor

INTRODUCTION

Vascular endothelial growth factor (VEGF) family consists of VEGF-A, placenta growth factor, VEGF-B, VEGF-C and VEGF-D, VEGF-E, VEGF-F, and their receptors: VEGF-1/Flt/1, VEGFR-2/KDR, and VEGFR-3/FLT-4. All these members have a common VEGF homology and play an essential role in fetal angiogenic development. VEGF is a soluble angiogenic factor produced by epithelial and stromal cells in the upper layers of the endometrium, whereas its receptors are expressed in the endothelial cells,

which can stimulate different endothelial functions. It is a strong mitogen for the endothelial cells derived from arteries, veins, and lymphatics but it lacks consistent and effective activity for other cells. The VEGF expression has been noticed in other tissues such as macrophages, keratinocytes, platelets, and renal mesangial cells.^[1-5]

The physiological changes in uterine circulation during early pregnancy are regulated by various hormones such as progesterone and human chorionic gonadotropin (hCG) secreted by syncytiotrophoblastic cells. They play an important role in the implantation process during pregnancy, such as cell growth and differentiation besides the maintenance of the corpus luteum. hCG hormones acting on the luteinizing hormone/hCG receptors produce many characteristic changes in the trophoblast cell phenotype and uterine vascularization that is required for the embryonic recruitment of the primate

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maternal circulation. hCG can stimulate the expression of VEGF. The VEGF expression increases significantly in syncytiotrophoblasts and decidua during pregnancy. It exhibits positive functional regulation by estrogen and progesterone in a steroid receptor-dependent manner. Thus, the formation, maintenance of the vascularization, and receptors of endometrium depend on angiogenesis and are promoted by the expression of VEGF and angiogenic factors such as angiopoietins. The progesterone and hCG appear to be regulating the expression of ovarian VEGF and also enhance vascularization and stabilization of corpus luteum in pregnant women.^[6-10]

There is an increase in the VEGF level during pregnancy could be due to trophoblastic villi which are generally hypoxic during the advancement interaction at early pregnancy; upkeep of sufficient blood dissemination was needed during placental development, and blood and oxygen supply is needed in the fetal development process. Various studies have shown that the VEGF and the expression of its receptor in placental tissue were identified during the whole pregnancy time frame and the intensity expanded with advancing pregnancy.^[11-13] In this study, we explored the correlation between the maternal serum VEGF levels and a fetal outcome such as birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, and growth/intrauterine growth restriction (IUGR).

MATERIALS AND METHODS

It is a comparative study conducted in the Department of Anatomy, and the subjects for the study were obtained from the Department of Obstetrics and Gynecology, Lady Hardinge Medical College. There were 120 pregnant females who were divided into a study and control group with equal distribution of 60 females each. The inclusion criteria for the study group subjects were as follows: (a) Pregnant females within the age of 20–35 years, (b) suffered three or more spontaneous abortions, (c) a single partner, and (d) no anatomical, physiological, hormonal, chromosomal, infective, or autoimmune causes for recurrent abortions identified previously. The control group females were (a) from same age group, (b) at least given birth to one live newborn, and (c) never suffered pregnancy loss previously. Further subjects suffering from diseases/disorders related to thyroid, autoimmunity, bleeding, endocrine, uterine, and congenital were excluded from the study. Written informed consent was received from all included females. A detailed general physical examination, relevant investigations, and ultrasound of the pelvis were carried out. The maternal serum VEGF levels were measured through the enzyme-linked immunoassay technique.

Statistical Analysis

The concentration of maternal serum VEGF levels was evaluated using the Student's *t*-test. $P < 0.01$ was considered statistically significant. The paired test was used to compare the relation between the maternal serum VEGF levels and fetal outcome factors such as APGAR score and birth weight.

RESULTS

The mean value of serum VEGF in the study group with adverse outcome, mean value of serum VEGF in the study group with normal outcome and mean value of serum VEGF in the control group with normal outcome was 450 pg/ml, 560 pg/ml and 1524 pg/ml respectively as shown in Table 1. The adverse outcome seen in the study group were pre-term delivery with low birth weight (5%), pre-term with normal birth weight (8.3%) and term delivery with intra-uterine growth retardation (8.3%). The correlation of VEGF with birth weight of the newborn was significant ($r = 0.282$, $P = 0.001$) as shown in Figure 1. The correlation of VEGF with APGAR score was very highly significant ($r = 0.285$, $P = 0.028$) as shown in Figure 2.

DISCUSSION

The VEGF has been written to be responsible for the adequate perfusion, oxygenation, nutrition, growth of the fetus, and placenta. It has also been mentioned to be a factor for mediating the maternal cardiovascular adaptation to pregnancy. The significant pregnancy-related hemodynamic changes incorporate expanded heart yield, increased blood volume, and diminished systemic vascular obstruction and blood pressure. These progressions add to the ideal development and advancement of the fetus and assist in protecting the mother from delivery complications. The decrease of serum VEGF levels may be related to inhibited fetal growth and development. In our study, we tried to determine the correlation between maternal serum VEGF levels and fetal outcomes such as birth weight, APGAR score, and growth. The mean maternal serum VEGF levels were higher in normal pregnancy and term pregnancy with normal weight/normal baby in comparison to the pre-term delivery with IUGR and underweight babies. There was a positive correlation between maternal serum VEGF and both birth weight and APGAR score.^[14-16]

There had been few studies conducted in the past on establishing the correlation we tried to establish in the present study. Here is a brief from the studies:

Birth Weight

In 1999, Wheeler *et al.* reported that serum VEGF concentrations were positively correlated with birth weight

Table 1: Serum VEGF levels and fetal outcome

Pregnancy and fetal outcome	Study group n=60 (%)	Control group n=60	Mean S. VEGF Conc. pg/ml
Pre-term delivery+LBW	3 (5)	-	485.38
Pre-term+NBW	5 (8.3)	-	546
Term delivery+IUGR	5 (8.3)	-	320
Term delivery with normal baby	47 (78)	-	560
Term delivery+normal birth weight	-	60	1524

VEGF: Vascular endothelial growth factor, LBW: Low birth weight, Mean value of serum VEGF in the study group with adverse outcome=486 pg/ml, mean value of serum VEGF in the study group with normal outcome=546 pg/ml, mean value of serum VEGF in the control group with normal outcome=1524 pg/ml

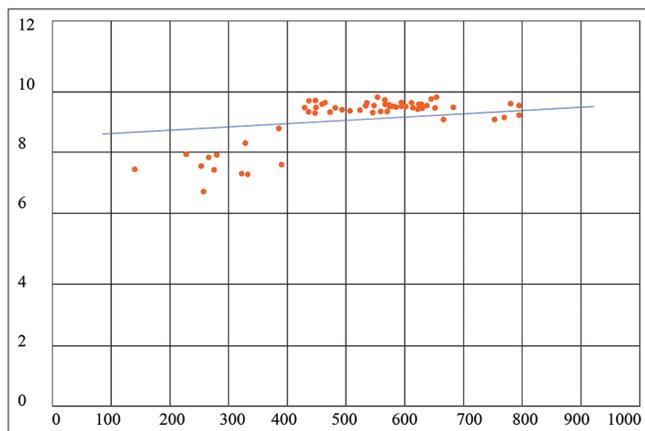


Figure 1: Scatter diagram showing positive correlation between serum vascular endothelial growth factor and Appearance, Pulse, Grimace, Activity, and Respiration score in recurrent abortion patients

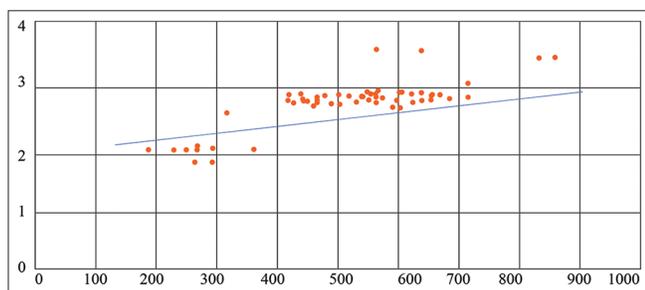


Figure 2: Scatter diagram showing positive correlation between serum vascular endothelial growth factor and birth weight in recurrent abortion patients

($r = 0.10, P = 0.02$), VEGF could be a factor for mediating the maternal cardiovascular adaptation to pregnancy. The maternal plasma VEGF levels were positively ($P < 0.05$) correlated with birth weight.^[17] In 2019, Tang *et al.* showed a positive correlation between the serum VEGF level and neonatal weight ($r = 0.435, P < 0.001$).^[18]

APGAR Score

In 2019, Tang *et al.* found a positive correlation between the serum VEGF level and Apgar score ($r = 0.357, P < 0.001$).^[18]

IUGR

In 2014, Darling AM found that the women who gave birth to SGA infants had notably lower median levels

of VEGF-A (9.43 pg/ml (interquartile range [IQR] 7.81, 85.38) vs. 51.08 pg/ml (IQR 7.81, 363.54)) women who gave birth to AGA infants.^[19] However, the studies conducted by Ariadne Malamitsi-Puchner *et al.* in 2005 and Kulkarni *et al.* in 2010 who showed that mothers giving birth to IUGR infants, the maternal serum VEGF levels were not found to correlate with the infant’s centile/birth outcome.^[20,21] Further, D. Borrás *et al.*, in 2014, found that maternal plasma f-VEGF was significantly higher in IUGR compared with controls ($p = 0.01$ and 0.001 , respectively).^[22]

The studies conducted in the past have shown results similar to our study with a positive correlation between birth weight and APGAR score but different results and observations as well when it comes to the relation between maternal serum VEGF levels and IUGR as some reporting positive relation and others no relation. The difference could be partially explained due to the difference in the use of total and free VEGF levels but there is a need to further investigate it with a large study.

Strengths

There is a paucity of research and literature pertaining to the subject published in the current article.

Limitations

The study sample size is small. It should be further tested with a bigger sample size for confirmation.

CONCLUSION

Based on our study, there is a positive correlation between maternal serum VEGF levels and fetal outcomes such as term delivery, birth weight, and APGAR score but it needs to be confirmed with a larger study.

ETHICAL STANDARD COMPLIANCE

Consent from Participants

Written informed consent was taken from all the participants.

Ethical Clearance

Ethical clearance was obtained from the Institution Ethical Committee.

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