

A Study on Endoglin Gene Impact in Recurrent Pregnancy Loss

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Abstract – Despite the reason, the drawn-out forecast of couples with recurrent pregnancy loss is acceptable, and most, in the end, accomplish a solid live birth. Be that as it may, numerous pregnancy losses can have a noteworthy mental cost for influenced couples. Numerous endeavours are being made to improve medicines and diminishing the time expected to accomplish a fruitful pregnancy. This article audits the setup, questionable etiologies, and suggested remedial systems, with an extraordinary spotlight on unexplained recurrent pregnancy losses and the empiric medicines utilized these days. It additionally examines the current job of preimplantation genetic testing in the administration of recurrent pregnancy loss.

Keywords – Impact, Endoglin gene, Pregnancy, Pregnancy loss

INTRODUCTION

Spontaneous abortion is a mind-boggling, multifactorial pathology, where different genetic, neural, endocrine, and immunological components are included. Cytokines, Toll-like receptors, and progesterone receptors assume basic jobs in early-stage implantation and advancement. A fragile, stage-explicit harmony of these proteins is required for fruitful pregnancy results. Be that as it may, genetic variety starting with one individual then onto the following outcomes in variety in levels of Th1/Th2 cytokines, quality of distinguishing proof of irresistible operators by Toll-like receptors, and nature of progesterone acknowledgement.

A basic advance in this procedure through the first and second trimesters is the infiltration of extravillous trophoblast (EVT) cells through the decidua and inward 33% of the myometrium, trailed by rebuilding of the winding supply routes. We are redesigning the uterine winding supply routes changes limited, high-opposition veins into enlarged, low-obstruction maternal blood courses into the intervillous space.

Early pregnancy loss is speculated to share comparative pathophysiology with toxemia originating from unusual placentation (11). In this way, we assessed the declaration of these seven proteins in EVT cells acquired by TRIC in examples from women with EPL and sound controls conveying at term.

RESEARCH METHODOLOGY

Patient Selection

The institutional audit leading group of Wayne State University endorsed this investigation, and each is taking an interest persistent gave educated assent. Patients were advised for an assortment of endocervical tests at Wayne State University or affiliated facilities. Rejection models included reasonable pregnancies with a background marked by vaginal dying. All the patients remembered for this investigation had a singleton pregnancy.

Endocervical Sampling

Endocervical inspecting was performed as depicted already somewhere else (32). Briefly, a vaginal speculum was utilized, and endocervical examples were gathered using a cytobrush and a ThinPrep unit (Hologic) containing 20 mL of PreservCyt fixative arrangement. The samples were moved to the research facility, where they were acidified with 500 mL of icy acidic corrosive for 5 minutes to break up the mucous. Samples then centrifuged.

Isolation of EVT Cells

The nonbound cells were gathered, trailed by three washings in 1 mL of PBS.

Immunocytochemistry

Slides containing segregated EVT cells were brooded for 17 hours at 4°C in Tris-crated saline containing 0.05. Tween-20 and 5 mg/mL cow-like serum egg whites (TTBS/BSA) with 10 mg/mL of mouse immune response against b-hCG, or 5 mg/mL of essential immunizer perceiving ENG, FLT1, AFP, PAPP-A, LGALS13, LGALS14, or PGF. The antibodies are depicted in Supplemental Table 2 (accessible on the web).

Protein Marker Quantification by Image Analysis

Fluorescent counteracting agent marking was imaged utilizing a Hamamatsu Orca cooled-chip advanced camera and a Leica DM IRB magnifying lens with filter sets for DAPI, FITC, and Texas Red. Cells in each field were imaged at a target magnification of 20 and a presentation season of 2.0 seconds. The FITC or Texas Red stain forces were quantified using

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is portrayed by the nearness of antiphospholipid antibodies (APL) and has for quite some time been related to RPL. Without a doubt, pregnancy dreariness is one of the two clinical standards required to affirm APS's diagnosis, the other being vascular apoplexy (Table 1). According to contemplates, APS's predominance in women with RPL fluctuates from as low as 6% to as high as 42%. However, it is commonly acknowledged to be 5%–20%. This is presumably clarified by utilising explicit measures of the nonstandardized research centre, and the various kinds of antibodies tried throughout the years. The main ones for diagnosing APS are lupus anticoagulant, anticardiolipin neutralizer, and hostile to 2 glycoproteins I. APS is alluded to as essential in patients with no hidden infection and optional for different conditions.

Genetic predisposition to URPL

Various genetic affiliation considers have been performed, and numerous up-and-comer qualities distinguished. An ongoing meta-examination that included 428 case-control reads discovered a relationship for 21 variations in 13 genes. Most of the qualities were engaged with resistant reaction, trailed by coagulation, digestion, and angiogenesis. Nonetheless, all the affiliations were unassuming, and none arrived at solid epidemiologic credibility—another meta-examination utilizing various measures discovered a critical relationship with 53 genetic polymorphisms of 37 genes. Interleukin qualities are the most regularly connected with RPL, particularly IL-1, IL-6, IL-10, and IL-18.

Immune dysregulation and URPL

In reality, the baby's safe maternal resistance is basic for typical implantation and pregnancy and is described by accepting administrative T cells and a calming Th-2 profile. Along these lines, an interruption of the typical CD4 T-aide cell (Th) and normal uterine executioner (NK) movement and a Th lopsidedness in the endometrium could prompt implantation disappointment and pregnancy loss. Immunomodulatory medicines have in this manner been proposed for women with URPL.

Sperm DNA fragmentation (SDF) and URPL

Standard semen boundaries don't appear to be related to the danger of pregnancy loss. However, in vitro and in vivo examinations have now indicated that a raised SDF contrarily influences richness, and it has been proposed as a reason for miscarriage. A meta-investigation of 16 associate reviews, including 2,969 couples, found a noteworthy increment in miscarriage in patients with high SDF. Two late partners consider discovered SDF, estimated with sperm chromatin scattering test, to be fundamentally higher in couples in the URPL bunch than a benchmark group of ripe men. Along these lines, it appears sensible to offer SDF testing to couples within any case URPL. Other than cutting edge fatherly age, numerous ecological variables, such as cigarette smoking, stoutness, exogenous warmth, and introduction to poisons, have been related to expanded SDF. Even though SDF is still not suggested by numerous social orders as a significant aspect of the workup for RPL,^{2,7} requesting the test could be valuable and could help fortify the choice to seek after way of life modifications.

Progesterone supplementation for URPL

Progesterone supplementation has been proposed as a treatment for URPL. Various arrangements, courses, portions, and durations have been accounted for. Yet, information from four preliminaries in women with at least three continuous miscarriages indicated that progesterone essentially diminished miscarriage rates contrasted with fake treatment or no treatment (chances proportion: 0.39; 95% CI: 0.21–0.72). The nature of the four preliminaries was, notwithstanding, thought to be poor. An ongoing multicenter, twofold visually impaired, fake treatment controlled preliminary haphazardly relegated 836 women with URPL to get either vaginal micronized supportive of progesterone (400 mg, twice day by day) or fake therapy following a positive pregnancy test and found no distinctions in LBR (65.8% versus 63.3%, individually).

PGS for URPL

PGS includes the investigation of every one of the 23 chromosome sets, with a few sub-atomic techniques utilized over the years, including ORGANISMS, CGH, exhibit CGH (aCGH), single-nucleotide polymorphism cluster, quantitative or ongoing polymerase chain response, and cutting edge sequencing, otherwise called monstrous equal sequencing. The qualities of every one of these techniques are past the extent of this audit; however, there are a few key contrasts, and the outcomes differ altogether. In short, ORGANISMS was the principal procedure utilized, and it permitted the assessment of a predetermined number of chromosomes (5–10) on blastomeres expelled from cleavage stage incipient organisms.

Workup

It is not prescribed to assess a couple tailing one miscarriage.¹⁰⁶ However, regardless of whether to start a full workup after two of three miscarriages has for some time been discussed. For quite a long time, it was prescribed to sit tight for three miscarriages; however, a few examinations have now demonstrated that the danger of a future miscarriage after two progressive losses (24%–29%) is like or marginally lower than the hazard after three losses (31%–33%), and the discoveries are comparable. Therefore, it is satisfactory to begin a workup following two back to back losses, particularly in women matured 35 years.

Alterations in the maternal Environment

The maternal condition changes incorporate anatomic uterine imperfections, endocrine inconsistencies, lopsided hormonal characteristics, disease, metabolic brokenness, wholesome lacks, safety issues and genetic factors.

EXPERIMENTAL RESULT AND DISCUSSION

Statistical Analysis and Data Modeling

Every single measurable investigation was performed utilizing JMP (adaptation 10.0; SAS Institute). Information was first inspected for ordinarity utilizing the Shapiro-Wilk test. The nonparametric Wilcoxon rank-entirety test examined between-bunch contrasts in RFU for every protein biomarker, as the information was not regularly appropriated. Spearman's rho was utilized to survey for the relationship among's GA and trophoblast yield. $P < .05$ was considered measurably significant.

Principal Component Analysis

The Principal Component Analysis (PCA) Score plot was created over the first two PCs, representing 75.8 of the all-out change, which isolated the EPL and control examples (Figure 1).

• Feed Intake of Dams during Pregnancy

The feed admission was comparative among gatherings and was as per the following: control (14.75 ± 1.45 g/d); PE (15.31 ± 1.60 g/d); PE+B12 (15.94 ± 1.15 g/d); PE+F (15.28 ± 0.76 g/d); PE+O (15.60 ± 0.79 g/d) and PE+B12+F+O (15.19 ± 1.83 g/d).

• Systolic and Diastolic Blood Pressure of Dams at the end of Pregnancy

The systolic and diastolic BP was comparative between bunches on d0 of pregnancy. Both systolic and diastolic BP were higher ($p < 0.01$ for both) on d19 of pregnancy in the PE bunch when contrasted with control.

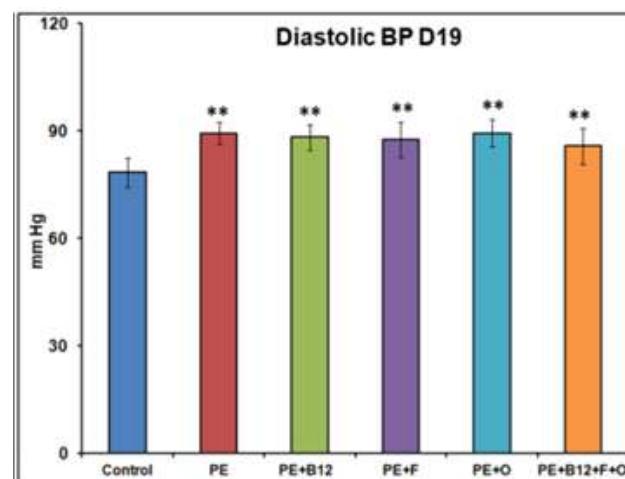
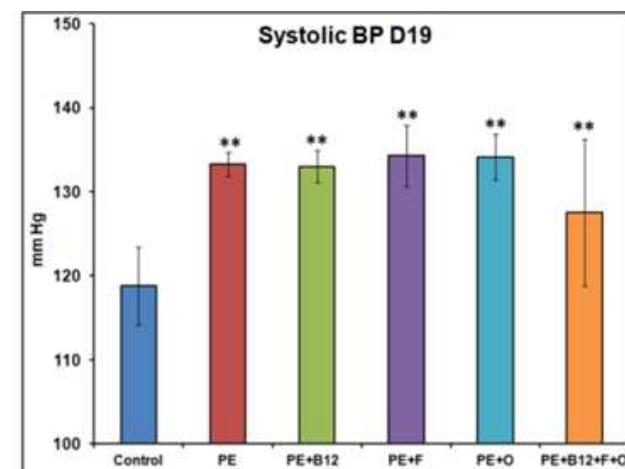


Figure 2: Systolic and Diastolic Blood Pressure of Dams at the end of Pregnancy

Growth Factors

The VEGF family (see Fig. 1) consists of VEGF-A, PIGF, VEGF-B, VEGF-C and VEGF-D as wells as their receptors VEGFR-1 (also called FLT-1), VEGFR-2 (also called KDR, in humans and fetal liver kinase, Flk, in mice; Waltenberger et al., 1994)

and VEGFR-3 (FLT-4), as well as the co-receptors, neuropilin-1 (NRP-1) and NRP-2.

Vascular endothelial growth factor-A The human VEGF-A gene has been assigned to chromosome 6p12-p21.1 (Mattei et al., 1996) and is organized as eight exons separated by seven introns (Houck et al., 1992). Alternative exon splicing results in six different isoforms VEGF-A 121, VEGF-A 145, VEGF-A 165, VEGF-A 183, VEGF-A 189 and VEGF-A 206 having 121, 145, 165, 183, 189 and 206 amino acids, respectively. VEGF-A 165 is the predominant isoform and native VEGF-A closely resembles VEGF-A 165 (Houck et al., 1992). VEGF-A binds with high affinity to two related receptor tyrosine kinases expressed on vascular endothelial cells (de Vries et al., 1992; Terman et al., 1992), FLT-1 and KDR (Waltenberger et al., 1994). Also, VEGF-A binds to NRP-1 and NRP-2.

VEGF-A mediates many functions in endothelial cells. VEGF-A promotes angiogenesis induces the growth of vascular endothelial cells (Ferrara and Davis-Smyth, 1997), reduces apoptosis (Zhou et al., 2003), mediated via the KDR/Flik1 receptor through the PI3-kinase/Akt signal transduction pathway (Gerber et al., 1998) and increases vascular permeability (Dvorak et al., 1995). In addition, VEGF-A promotes vasodilatation via the endothelial-derived nitric oxide pathway.

Hypoxia is a potent stimulus for the expression of VEGF-A mRNA and is mediated via hypoxia-inducible-factor-1a (Taylor et al., 1997; Semenza 2002). In addition, several growth factors, including fibroblast growth factor, transforming growth factors (TGF- α and TGF- β), keratinocyte growth factor, insulin-like growth factor 1 (IGF-1) and platelet-derived growth factor, as well as the inflammatory cytokines, interleukin (IL)-1 α and IL-6 is also known to up-regulate VEGF-A expression (Ferrara and Davis-Smyth, 1997; Neufeld et al., 1999).

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• Reproductive Performance

The absolute weight addition of dams in the PE bunch was tantamount to control. Thus supplementation with particular micronutrients like folate (PE+F), nutrient B12 (PE+B12) or omega-3 (PE+O) unsaturated fats and a joined micronutrient and omega-3 unsaturated fat supplementation (PE+B12+F+O) additionally didn't influence the weight increase of dams during pregnancy and was practically identical to control.

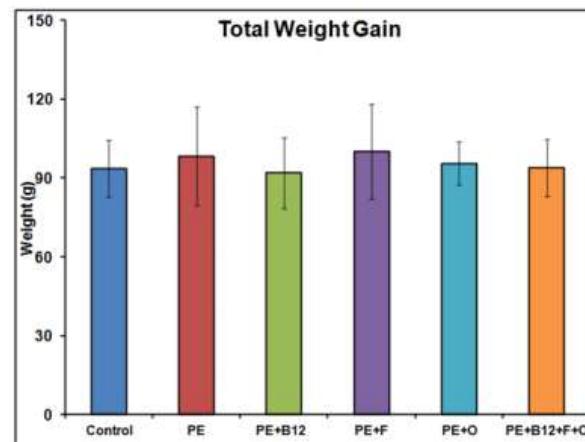


Figure 3: Reproductive Performance of Dams during Pregnancy

Values are expressed as Mean \pm SD; p: Level of Significance; *p<0.05, **p<0.01 as compared to control

The litter size in all the gatherings was practically identical to control. Litter weight is the normal load of the considerable number of litters during childbirth and was not influenced by preeclampsia. The current examination toxemia demonstrated a pattern for decreasing litter weight even though it didn't arrive at centrality. The litter size was higher (p<0.05) in the PE+O bunch compared to the control. Interestingly, PE bunch indicated decreased (p<0.01 for all) little guy weight in all gatherings when determined with control and didn't improve either by an individual or a consolidated micronutrient and omega-3 unsaturated fat supplementation to PE gathering.

- Absolute and Relative Weights of Liver and Brain of Dam at the end of Pregnancy**

In dams, outright and relative liver loads were equivalent between the gatherings. Omega-3 unsaturated fat supplementation to dams with PE (PE+O) expanded (p<0.05) the outright just as relative cerebrum loads when contrasted with control.

Also, maternal folic corrosive supplementation to dams with PE (PE+F) (p<0.05 for all) expanded the outright cerebrum loads when contrasted with control, PE and PE+B12 gatherings (Table 1).

Table 1: Absolute and Relative Organ Weights of Dams on d20 of Pregnancy

	Control	PE	PE+B12	PE+F	PE+O	PE+B12+F+O
Absolute Weight (g)						
Liver	9.45 \pm 1.16	8.89 \pm 1.27	8.81 \pm 1.08	9.49 \pm 0.63	9.06 \pm 0.94	9.31 \pm 0.58
Brain	1.76 \pm 0.12	1.77 \pm 0.09	1.78 \pm 0.09	1.90 \pm 0.06 ^{**}	1.86 \pm 0.07	1.78 \pm 0.12 ^{**}
Relative Weight (%)						
Liver	3.14 \pm 0.36	2.97 \pm 0.29	2.96 \pm 0.26	3.13 \pm 0.14	3.01 \pm 0.25	3.14 \pm 0.13
Brain	0.58 \pm 0.04	0.59 \pm 0.03	0.60 \pm 0.03	0.62 \pm 0.02 [*]	0.62 \pm 0.02 [*]	0.60 \pm 0.02

- Dam Plasma Vitamin B12, Folic Acid and Homocysteine Levels at the end of Pregnancy**

The levels of plasma nutrient B12 were similar to control in the PE gathering, while that of folate was lower (p<0.01) when contrasted with control. Interestingly, the degrees of plasma homocysteine were higher (p<0.05) in the PE than in the control.

Maternal nutrient B12 supplementation to PE gathering (PE+B12) expanded (p<0.01) the degrees of plasma nutrient B12. Be that as it may, it couldn't standardize the degrees of homocysteine and brought down (p<0.05) the plasma folate levels when contrasted with control.

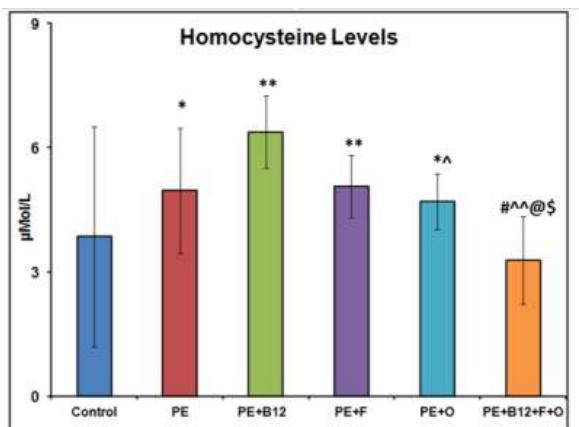
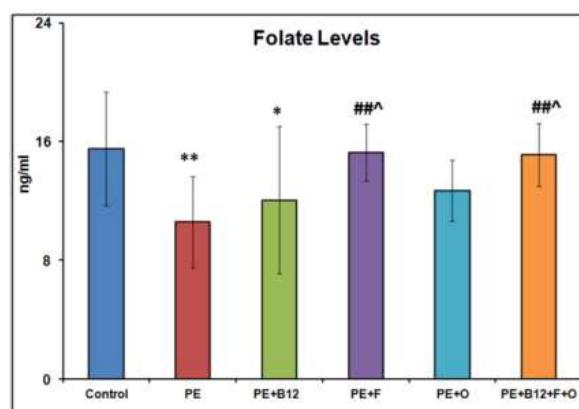
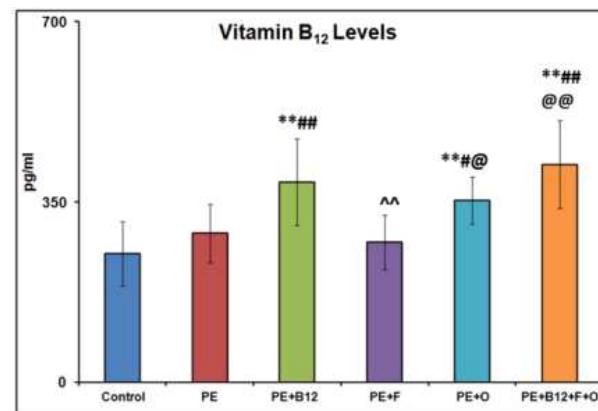


Figure 4: Dam Plasma Vitamin B12, Folate and Homocysteine Levels on d20 of Pregnancy

A joined maternal micronutrient and omega-3 unsaturated fat supplementation to dams with PE (PE+B12+F+O) expanded (p<0.01) the degrees of plasma nutrient B12 and standardized the degrees of homocysteine to that of control. Levels of plasma folate in this gathering were additionally practically identical to control (Fig.4).

4.3.6 Dam Plasma MDA Levels at the end of Pregnancy

Toxemia expanded (p<0.01) the plasma MDA levels when contrasted with control. Conversely, maternal nutrient B12 supplementation (PE+B12), maternal omega3 unsaturated fat supplementation (PE+O) and a consolidated maternal micronutrient

and omega-3 unsaturated fat supplementation (PE+B12+F+O) to dams with PE had the option to lower ($p<0.05$ for all) the plasma MDA levels when contrasted with PE gathering however not when contrasted with control (Figure 5).

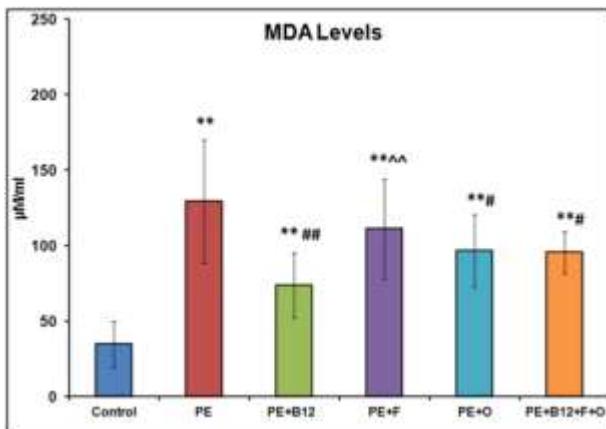


Figure 5: Dam Plasma MDA Levels on d20 of Pregnancy

- Levels of Glucose, Cholesterol and Triglycerides in the Dam Plasma at the end of Pregnancy**

Plasma glucose levels in dams with PE were practically identical to control. Maternal nutrient B12 (PE+B12), folate (PE+F) or omega-3 unsaturated fat supplementation (PE+O) didn't change the degrees of plasma glucose as they stayed practically identical to control. Interestingly, consolidated maternal micronutrient and omega-3 unsaturated fat supplementation (PE+B12+F+O) expanded ($p<0.05$) the plasma glucose levels when contrasted with the PE gathering.

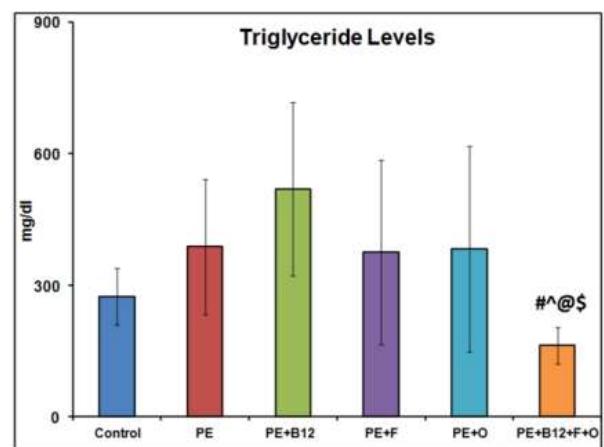
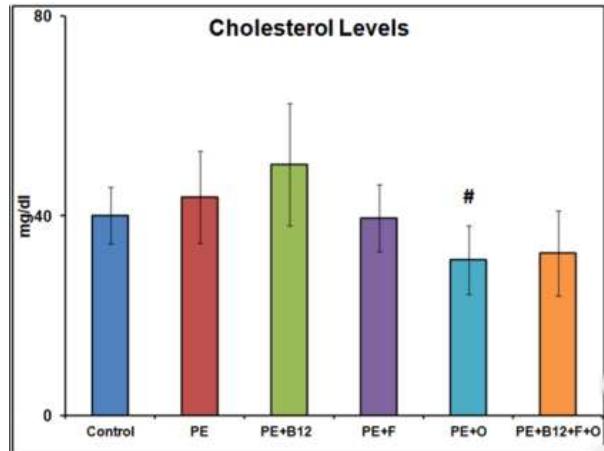
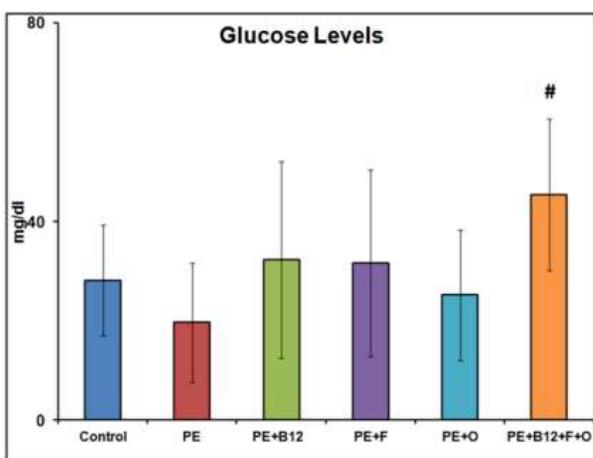


Figure 6: Levels of Glucose, Cholesterol and Triglycerides in the Dam plasmaat the end of Pregnancy

Toxemia expanded the dam plasma levels of fatty substances when contrasted with control even though it was not measurably critical. Maternal nutrient B12 (PE+B12), folate (PE+F) and omega-3 unsaturated fat supplementation (PE+O) didn't bring down the plasma fatty oils. Interestingly, joined maternal micronutrient and omega-3 unsaturated fat supplementation (PE+B12+F+O) to dams with PE decreased ($p<0.05$ for all) the plasma fatty oil levels when contrasted with PE gathering (Fig.4.5).

- Results of Placenta at d20 of Pregnancy**

Maternal folate supplementation to dams with PE (PE+F) had the option to standardize levels of DHA when contrasted with control however demonstrated higher ($p<0.05$ for both) DHA levels when contrasted with PE gathering. Maternal omega-3 unsaturated fat supplementation to dams with PE (PE+O) brought down ($p<0.01$ for all) the degrees of AA and expanded ($p<0.01$ for all) DHA when contrasted with control, PE, PE+B12 and PE+F bunches in the placenta. A joined maternal micronutrient and omega-3 unsaturated fat supplementation (PE+B12+F+O) likewise brought

down ($p<0.05$ for all) the degrees of AA when contrasted with PE, PE+B12 and PE+F gatherings. Conversely, levels of DHA in the placenta in this gathering were higher ($p<0.01$ for all) when contrasted with all other treatment gatherings (Fig.4.6).

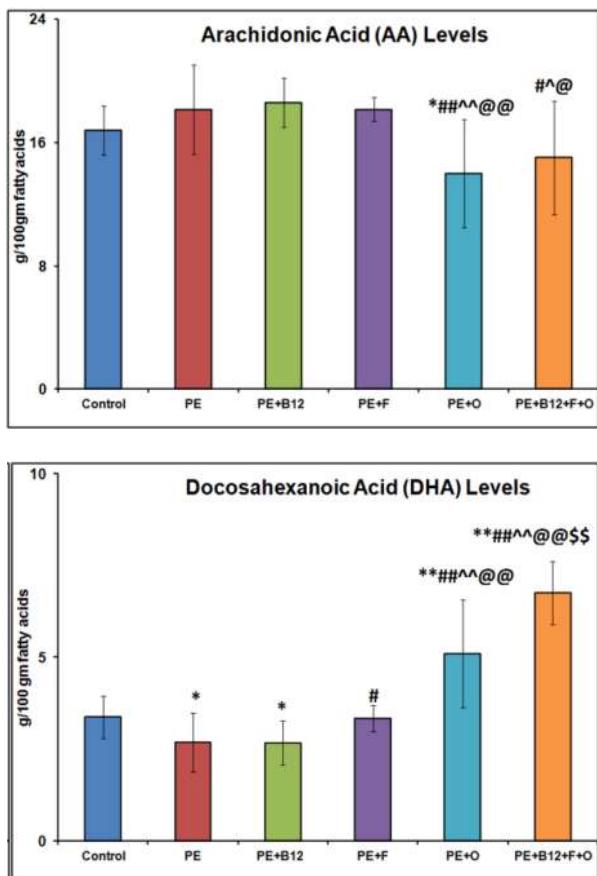


Figure 7: Fatty Acid Levels in the Placenta at d20 of Pregnancy

CONCLUSION:

The procedure of assimilation whereby individuals move to an alternate social setting may likewise impact the job of RELATIONSHIP as discoveries might be like the individuals who had consistently lived in that specific social setting. In light of this, it is essential to see how men from shifting RELATIONSHIPS are affected by despondency following a pregnancy loss and how they manage this sorrow in their particular social settings. Likewise, it is indispensable to investigate pregnancy loss from the point of view of non-hetero non-cisgender men, as examination with these populaces is inadequate. Moving toward men's encounters of pregnancy loss from a biopsychosocial perspective may prompt a superior comprehension in social insurance of how pregnancy loss may affect men both genuinely and intellectually, which may impact the advancement of improved practices and assets.

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