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Role of low vitamin d3 levels and linked deregulated placental apoptosis in recurrent pregnancy loss (RPL) pathogenesis: a study from northeast India

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Context: RPL is a global problem including northeast India; and the underlying molecular etiology associated with it is poorly documented.
Objective: Given the role of vit D in apoptosis, we aimed to delineate the role of differential serum vitD (vitD3) and vit D receptor (VDR) expression modulated differential apoptosis profile and its probable mechanism associated with RPL pathogenesis.
Methods: Serum VitD3 levels were evaluated by ELISA. Differential placental apoptosis levels were studied by MUSE based flowcytometry approach. Differential expression of the VDR and candidate genes of apoptotic pathways were studied using qPCR. TNFRSF6 (fas receptor) A670G gene polymorphism was studied by PCR-RFLP.
Patient(s): Blood and Product of conception (POCs) tissue samples were collected from RPL (n=35) and medically terminated pregnancy cases (MTP,n=40), along with placental tissues from term delivery subjects(TD,n=52).
Intervention(s):None
Main Outcome Measures:Pregnancy outcome
Results: All pregnancy cases were of severe VitD3 deficient category, and its levels in RPL cases were down-regulated compared to both TD(p=0.065) and MTP cases(p=0.033). VDR expression was downregulated in RPL cases compared to both TD(0.072±0.028folds) and MTP(0.227±0.11folds).Significant increase in placental apoptosis cell counts percentage was observed in RPL cases(21.94±6.733%) compared to both MTP(1.829±0.739%)(p<0.001) and TD(2.945±1.032%)(p<0.001). Sharp upregulation in the fasR, fasL and caspase3 expression was observed in RPL cases compared to MTP cases; and caspase3 expression correlated positively with expression of fasR and fasL but not with caspase9 and bcl2. Both lower serum vitD3 levels and down-regulated VDR mRNA expression correlated negatively with fasR and fasL expression, and moreover significantly correlated with deregulated placental apoptosis levels. Presence of variant G allele of TNFRSF6 was associated with reduced (i)risk of RPL compared to TD[OR=0.593, p=0.264] and MTP[0.642,p=0.473] cases, (ii)expression of fasR mRNA in RPL cases(p=0.177), indicating the protective nature of the variant G allele against RPL susceptibility.
Conclusions: Lower serum VitD3 levels and decreased placental VDR expression is associated with upregulated fasL-fasR-caspase3 death receptor-driven extrinsic apoptotic pathway mediated increased placental apoptosis leading to RPL. TNFRSF6 gene variant G allele is associated with reduced risk of RPL, and has prognostic significance.

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