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Detrimental effect of progesterone pathway deregulation modulated immune activation in preterm delivery and outcome in hepatitis e virus (hev) infected pregnancy cases from northeast india

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Context: HEV infection is severe during pregnancy and is associated with both fetal and maternal mortality, although the candidate mechanism is still far from being characterized. Molecular endocrinological parameters and linked immunomodulation are known to influence pregnancy outcome.
Objectives: To evaluate the association of Progesterone pathway deregulation(s) and linked altered immunomodulation in HEV infected pregnancy complications such as preterm delivery (PTD) and outcome.
Methods: Distribution of PR mutation was studied by PCR. Differential mRNA expression of progesterone receptor (PR) and PIBF was evaluated by qPCR. NK-NKT cell profiling was studied by FACS. Serum and placental levels of cytokines were evaluated by ELISA and qPCR respectively.
Patient(s): A total of 38 HEV infected pregnancy cases categorized as AVH (Acute Viral Hepatitis, N=25) and FHF (Fulminant Hepatic Failure cases, N=13) were enrolled along with 194 term delivery (TD) with informed consent.
Intervention(s):None
Main Outcome Measure(s):Delivery
Result(s): PR mutation was significantly higher in PTD cases (p=0.021) and was associated with increased risk of PTD in HEV infected pregnancy cases [OR=6.33, p=0.076] as well as with negative outcome i.e. fetal death in PTD cases. The PR (p=0.005) and PIBF (p=0.007) mRNA expression was significantly down-regulated in HEV PTD cases, and in cases with fetal death. Average NK cell count was higher in both AVH and FHF PTD groups within their respective cohort than TD cases. A distinct Th1 biased state was observed in HEV cases showing significant up-regulation of TNF-? (p<0.001). and IFN? (p=0.034), with downregulation of Th2 type IL-10 (p<0.001). TNF-? levels was higher in AVH PTD cases compared to AVH TD cases. Proinflammatory NF-??p65 in placenta at mRNA level was upregulated in HEV cases and was associated with fetal death. Placental PR mRNA expression inversely correlated with NF-??p65 expression, and placental TNF? expression positively correlated with NF-??p65 expression; thereby underlyning the importance of deregulation of PR pathway in HEV-PTD cases.
Conclusions: Genetic and expression changes in key PR pathway components and associated Th1 biased altered immunomodulation status predisposes HEV infected pregnancy cases to PTD and negative pregnancy outcome. Thus PR and PIBF expression, TNF-? and IL10 levels may both suitably serve as biomarkers to be used for stratifying pregnancy cases with risk of preterm delivery.

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