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BRAIN PROTECTION BY TRANSAMNIOTIC STEM CELL THERAPY (TRASCET) IN A MODEL OF INTRAUTERINE GROWTH RESTRICTION (IUGR)

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Purpose: Transamniotic stem cell therapy (TRASCET) with mesenchymal stem cells (MSCs) has been shown experimentally to reverse some of the effects of intrauterine growth restriction (IUGR), apparently by attenuating placental inflammation. Neurodevelopmental deficits driven by neuroinflammation are major complications of IUGR. We sought to determine whether MSC-based TRASCET also mitigates inflammation in the fetal brain.

Methods: After IACUC approval, pregnant Sprague-Dawley dams (n=8) were exposed to alternating 12-hour hypoxia (10.5% O2) cycles from gestational day 15 (E15) until term (E21). One group remained untreated (n=28 fetuses). Three groups received volume-matched intra-amniotic injections into all fetuses (n=68) of either saline (sham; n=19), or a suspension of amniotic fluid-derived MSCs, either in native state (TRASCET; n=20), or primed by exposure to interferon-gamma (IFN-γ) and interleukin-1beta (IL-1β) for 24 hours prior to administration in vivo (TRASCET-Primed; n=29). Donor MSCs were syngeneic Lewis rat cells phenotyped by flow cytometry. Normal fetuses served as controls (n=20). Multiple analyses were performed at term, including ELISA in fetal brains for the pro-inflammatory cytokines transforming growth factor-alpha (TNF-α) and IL-1β. Statistical comparisons were by Wilcox-rank sum test, including Bonferroni-adjusted significance.

Results: Overall survival was 75% (88/116). Gross brain weights were significantly decreased from normal in both the untreated and sham groups (both $p<0.001$) and significantly increased in both TRASCET groups when compared to untreated and sham ($p=0.003$ to <0.001; figure). TRASCET-Primed led to significantly lower levels of TNF-α and IL-1β compared to untreated (both $p<0.001$) and sham ($p=0.017$ and $p=0.011$, respectively). Unprimed TRASCET led to significantly lower levels of TNF-α and IL-1β compared to untreated ($p=0.009$ to <0.001), but not sham ($p=0.133$ and $p=0.973$, respectively).

Conclusions: Transamniotic stem cell therapy with primed mesenchymal stem cells reverses some of the central nervous system effects of intrauterine growth restriction in a rat model, possibly by modulating neuroinflammation.