



Placental ageing in term small for gestational age and growth restricted fetuses

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Objective

From early to term pregnancy, the placenta normally suffers of aging promoting cell death leading to decreased activity related to normal post-term changes. While previous studies in placentas from small fetuses suggested an accelerated placental aging process, it is unclear whether SGA -with apparent normal placental function by ultrasound- encompass premature placental aging or whether this phenomenon is restricted to FGR. The aim of this study was to perform a comprehensive assessment of the placental aging process through senescence and apoptotic markers in late-onset small fetuses classified as SGA or FGR.

Methods

A nested case-control study in singleton pregnancies delivering at term including 21 normally grown fetuses and 36 small fetuses classified into SGA (if birthweight was between the 3rd and 9th centile and normal fetoplacental Doppler; n=18) and FGR (if birthweight <3rd centile and/or abnormal cerebroplacental ratio or uterine artery Doppler; n=18). Telomerase activity, telomere length and RNA expression of senescence (Sirtuin 1, 3, 6) and apoptotic markers (p53, p21, BAX, Caspase 3 and 9) were analyzed in placental samples collected at birth.

Results

Compared with normally grown fetuses, both SGA and FGR presented signs of accelerated placental aging including lower telomerase activity (controls mean \pm SD 12.8% \pm 6.6 vs SGA 7.98% \pm 4.2 vs FGR 7.79% \pm 4.6, p=0.008), shorter telomeres (controls 1.20 T/S \pm 0.6 vs SGA 1.08 T/S \pm 0.9 vs FGR 0.66 T/S \pm 0.5, p=0.017), and reduced Sirtuin1 RNA expression (controls 1.55 2- $\Delta\Delta$ Ct \pm 0.8 vs SGA 0.91 2- $\Delta\Delta$ Ct \pm 0.8 vs FGR 0.63 2- $\Delta\Delta$ Ct \pm 0.5, p<0.001) together with increased p53 RNA expression (controls median(IQR) 1.072- $\Delta\Delta$ Ct (3.2) vs SGA 5.39 2- $\Delta\Delta$ Ct (15) vs FGR 3.75 2- $\Delta\Delta$ Ct (7.8), p=0.040), with a significant linear tendency across severity stages. In addition, FGR cases presented signs of apoptosis with increased RNA levels of Caspase 3 (controls 0.94 2- $\Delta\Delta$ Ct (1.1) vs FGR 3.98 2- $\Delta\Delta$ Ct (30), p=0.031) and Caspase 9 (controls 1.21 2- $\Delta\Delta$ Ct (4.0) vs FGR 3.87 2- $\Delta\Delta$ Ct (8.7), p=0.037) as compared to controls.

Conclusion

A comprehensive assessment demonstrated accelerated placental aging in both clinical forms of late-onset fetal smallness, supporting a common pathophysiology and challenging the concept of SGA being 'constitutionally small'.