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Obesity effects on female fertility, embryo development and programming metabolism in the next generation

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Obesity in women is associated with impaired fertility and understanding the molecular defects underpinning this pathology is essential as obesity rates increase globally. Obesity is associated with systemic insulin resistance and metabolic syndrome, and similar changes occur within the ovary, with increased insulin and triglyceride surrounding the developing oocytes. The ovary contains a finite number of oocytes, and their release at ovulation becomes sporadic and disordered with obesity onset, contributing to loss of fertility. We identify that fibrosis within the central stromal compartment of the ovary is an underlying mechanism responsible for impaired oocyte release; that is initiated by mitochondrial dysfunction leading to diminished bioenergetics, oxidative damage, inflammation and collagen deposition. Further, anti-fibrosis drugs eliminate fibrotic collagen and restore ovulation in reproductively old and obese mice, in association with dampened M2 macrophage polarization and upregulated MMP13 protease. This is the first evidence that ovarian fibrosis is reversible and indicates that drugs targeting mitochondrial metabolism may be a viable therapeutic strategy for women with metabolic disorders (or advancing age) to maintain ovarian function and extend fertility.

Obesity-induced mitochondrial dysfunction also occurs in granulosa cells of the ovary which directly surround the oocyte. Mitochondrial respiration, but not glycolysis, was reduced in granulosa cells of obese mice; and female mice that were both obese and reproductively old showed a marked decrease in both mitochondrial respiration and glycolysis. To translate these findings, the metabolic profile of granulosa cells was measured in a cohort of 130 women undergoing IVF/ICSI cycles, and correlated with clinical parameters and cycle outcomes. Increased BMI resulted in significant alterations in granulosa cell metabolic profile, and further, distinct aspects of the follicular metabolic profile were correlated with IVF outcomes particularly successful fertilisation. These results provide new insights into the cellular mechanisms of subfertility, by demonstrating specific metabolic perturbations that are associated with poor oocyte quality in women.

Within the cumulus oocyte complex, our studies in mice show that insulin resistance and hyperlipidemia lead to endoplasmic reticulum stress and altered mitochondrial activity in oocytes. In vitro fertilization of oocytes from obese mice demonstrates their impaired developmental potential and marked mtDNA loss by the blastocyst stage. Subsequently, fetuses from obese oocytes were heavier than controls and had reduced liver, heart and kidney mtDNA content. Treatment of the obese females with ER stress inhibitor salubrinal or the chaperone inducer BGP-15 immediately prior to IVF normalized oocyte mitochondrial activity as well as subsequent blastocyst development, fetal weight and fetal tissue mtDNA content. These results demonstrate that obesity in mothers imparts a legacy of mitochondrial loss in offspring, that is due to cellular stress during oocyte maturation but that is preventable prior to conception.

Despite extensive attention, obesity rates continue to increase worldwide particularly in children. Accumulating evidence conclusively demonstrates that key aspects of metabolism are ‘programmed’ prior to birth, placing children of obese parents at particularly high risk. Fortunately, our understanding of the underlying cellular events that mediate this developmental programming is rapidly expanding. Obesity in would-be parents alters both egg and sperm as well as every stage of embryo development, through modulation of distinct molecular pathways. Understanding this profound biology provides the basis for new clinical interventions and progressive policy changes.