Follicular fluid from overweight women displays altered energy metabolism and oocytes with smaller sizes

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Overweight is a condition associated with obesity, impacting half of the population in Brazil. Moreover, there is a concerning trend suggesting that more than half of the global population could be obese by the year 2035. On the other hand, infertility is a prevalent condition, with recent research estimating that one in six individuals will experience infertility during their lifetime. Given the increasing prevalence of these two conditions, it is becoming more common to encounter overweight women seeking assisted reproduction treatment. It is well-established that obesity adversely affects the retrieval of oocytes, leading to a low fertilization rate, a high concentration of lipids in follicular fluid (FF), and the production of poor-quality embryos. However, identifying the underlying causes of these effects remains challenging. In this study, we explore the metabolic aspects of the follicular environment in overweight infertile women and its impact on oocytes and embryos. Recognizing the limited number of studies focusing on individual follicles and their follicular fluid, we conducted a single-center prospective analysis from March 2022 to August 2022, involving 20 patients. The recruitment was based on their Body Mass Index (BMI), leading to the formation of two groups: Normal BMI (NBMI) ranging from 18.5 to 24.9 kg/m² and High BMI (HBMI) ranging from 25 to 29.9 kg/m². Among the participants, 13 fell into the NBMI category, while 7 belonged to the HBMI category. Exclusion criteria encompassed patients with Polycystic Ovary Syndrome (PCOS), ovarian insufficiency, Endometriosis in stages III and IV, and those who had undergone prior treatments at the clinic. During the oocyte retrieval day, we conducted a meticulous puncture of follicles individually, followed by system washing. Only follicular fluid without visible blood contamination and with the presence of oocytes was utilized, and no pooling of fluids was performed. FF were analyzed for glucose, lactate, insulin, and MDA (an important oxidative stress marker). Morphokinetic assessments were conducted for all embryos (total of 81) and the diameter of matured oocytes were collected (117 oocytes). Women with High BMI (HBMI) exhibited higher levels of insulin and a twofold increase in lactate (p=0.017, p=0.01, respectively). Unexpectedly, Normal BMI (NBMI) women showed a higher amount of MDA (p=0.004), while glucose levels did not differ significantly (p=0.64). Regarding morphokinetic parameters, the Time of pronuclear fading was longer in embryos from HBMI women (p=0.003). Mature oocytes from HBMI individuals were found to be smaller compared to those from NBMI individuals (p=0.03). The observed increase in insulin in the follicular fluid (FF) was expected to result in higher glucose consumption. Consequently, cumulus cells likely reduced the glycolysis rate, transitioning to the Warburg effect, which may explain the elevated levels of lactate found in the FF. In individuals with Normal BMI (NBMI), the standard glycolysis and

tricarboxylic acid (TCA) cycle process generates reactive oxidative species, resulting in increased Malondialdehyde (MDA) in follicular fluid (FF). The insufficient energy consumption likely contributed to smaller oocytes and delayed pronuclear fading. This study is the first to identify, through the analysis of individual follicular fluids, a shift in energy metabolism, revealing the Warburg effect in cumulus cells. Notably, the Warburg effect is typically associated with cancer cells and embryos. However, more studies involving a larger patient cohort are essential to validate this hypothesis, explore its impact on clinical outcomes, and delve into the metabolic dynamics of embryos.

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