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L-carnitine restores mitochondrial function of human embryos decreased with female donor age.

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Study question: Does L-carnitine restore an adverse effect of female donor age on the mitochondrial function of their embryos?
Summary answer: Mitochondrial function at morula stage of human embryos decreased with their female-donor age and L-carnitine restored the mitochondrial function and the development of human embryos.
What is known already: Although the rates of oxygen consumption (OCRs) of human embryos increases with their development, the relationship between female donor age and mitochondrial function of their embryos remains obscure. L-carnitine plays important roles in reducing the membranous toxicity of free fatty acids by forming acyl-carnitine and promoting beta-oxidation, leading to alleviation of cell damage. Recent studies have shown that L-carnitine also plays important roles in in vitro oocyte growth, oocyte maturation, and embryonic development. However, whether such beneficial effects of L-carnitine lead to an improvement of mitochondrial function remains unknown.
Study design, size, duration: Fourteen oocytes and 106 embryos were used to assess mitochondrial DNA (mtDNA) copy numbers and OCRs and to examine the effect of L-carnitine. All specimens were obtained between July 2004 and June 2016, and donated from couples after they had given informed consent. The development of 374 embryos was retrospectively analyzed to assess the effects of female donor age. The development of 1308 zygotes cultured in medium with or without L-carnitine was prospectively analyzed.
Participants/materials, setting, methods: Mature oocytes and developed embryos to 6-8 cell, morula and blastocyst stages were used to assess their OCRs and mtDNA copy number. The relationships between female donor age and OCRs, and female donor age

and mtDNA copy number were analyzed. Effect of L-carnitine was also assessed similarly. Using clinical data, the developmental rate from morula to blastocyst was compared among 3 different age groups and effect of L-carnitine on the blastocyst development was examined.

Main results and role of the chance: Although there were no relationships between female donor age and mtDNA copy number in any stages, the OCRs of morulae decreased with female donor age (r^2 = 0.45, P < 0.01). An addition of l-carnitine increased the OCRs of morulae (1.18 fmol/sec) compared with their sibling embryos (1.08 fmol/sec, P < 0.05). In clinical data analysis, the developmental rate from morula to blastocyst decreased with female donor age (P < 0.05, < 35 yo: 75.6% vs. 35-40 yo: 70.4% vs. > 40 yo: 46.8%). An addition of L-carnitine into a culture medium significantly improved the morphologically-good blastocyst rate per fertilized ova (P < 0.01, 15.1%) compared with their sibling embryos (8.8%). Twenty healthy babies were born from blastocysts cultured in L-carnitine-supplemented medium after single blastocyst transfer.
Limitations, reason for caution: Large-scale studies should be required to assess whether an addition of L-carnitine improves the development of embryos obtained from older women. Aneuploidy has not been assessed in accordance with clinical guideline of the Japan Society of Obstetrics and Gynecology.
Wider implications of the findings: The data of the present study revealed that mitochondrial function (OCRs) at morula stage of human embryos decreased with their female donor age. L-carnitine restored the mitochondrial function and the development of human embryos.
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Trial registration number: This study was approved by the IRB of IVF Namba Clinic and registered by the Japan Society of Obstetrics and Gynecology (Registry numbers 135 and 138).