P-146 Differential impact of three embryo culture media for IVF on in vitro development and perinatal outcome: a single-center RCT

M. Murakami[1], K. Tanaka[2], H. Otsubo[2], S. Mizumoto[2], Y. Nagao[2], T. Kuramoto[3]

[1]Kuramoto Women's Clinic, Research laboratory, Fukuoka, Japan ; [2]Kuramoto Women's Clinic, IVF laboratory, Fukuoka, Japan ; [3]Kuramoto Women's Clinic, President, Fukuoka, Japan

Study question: This report provides updated data from an RCT determining which embryo culture medium yields optimal IVF outcomes.

Summary answer: Embryo culture systems used for IVF differentially affected preimplantation development and resultant obstetric and perinatal outcomes, including birthweights of live-born singletons.

What is known already: Currently, multiple embryo culture medium systems are in use for IVF, raising questions regarding which is optimal. However, the ability of a medium to yield preimplantation embryos is not necessarily indicative of embryo viability. For example, supplementation of medium with serum was commonly used to increase animal blastocyst yields, but this impaired embryonic, fetal, and offspring health. In humans, medium composition and culture duration can influence IVF efficacy and offspring phenotype. Given the importance of culture systems in determining clinical outcomes, existing data regarding differential culture system impacts are insufficient and additional well-designed studies are required.

Study design, size, duration: Between February 2016 and August 2017, 795 couples undergoing their first autologous clinical IVF cycle and freeze-all strategy were recruited. Participants were randomized via computer-generated tables into three groups. Following standard oocyte retrieval and IVF/ICSI procedures, embryos were cultured using three different culture media, G1 Plus/G2 Plus (G1/G2; Vitrolife), Global Total (GT; LifeGlobal), or Sequential Cleav/Sequential Blast (SC/SB; Origio). Thirty-eight patients exhibiting no 2PN oocytes following insemination or those undergoing fresh embryo transfers were excluded.

Participants/materials, setting, methods: For patients yielding a single good-quality cleavage-stage (day-2 or day-3) embryo, that cleavage-stage embryo was vitrified. For patients yielding two or more good-quality cleavage-stage embryos, two or less good-quality cleavage-stage embryos were vitrified. The culture period of the remaining embryos was extended, and all good-quality blastocyst-stage (day-5 or day-6) embryos were vitrified. This report presents data for vitrified embryo transfer performed until the end of December 2020.

Main results and the role of chance: The mean per-cycle vitrified embryo yield (± SD) was comparable between groups for cleavage-stage embryos, but significantly different for blastocyst-stage embryos (G1/G2: 1.69 ± 2.2, GT: 2.53 ± 3.01, SC/SB: 2.04 ± 2.42; P = 0.001). Following vitrified cleavage- or blastocyst-stage embryo transfers, biochemical pregnancy rates were significantly different between groups (G1/G2: 55.6 %, GT: 59.1 %, SC/SB: 46.2 %; P = 0.011). Furthermore, a between-group trend towards different live birth rates was observed (G1/G2: 41.7 %, GT: 42.1 %, SC/SB: 33.1 %; P = 0.063). Of 382 live births, data for first-borns (n = 323; 295 singletons and 14 twin-pairs) are reported here. Perinatal data did not differ significantly between groups for both cleavage- and blastocyst-stage embryo transfers, including gestational age- and gender-adjusted singleton birthweight (z-score). Following multiple linear regression (including selected covariates), adjusted mean singleton birthweights were

significantly lower in the G1/G2 and GT groups than in the SC/SB group (by 131 g; P = 0.011 and 110 g; P = 0.032, respectively) and tended to be lower for cleavage-stage embryo transfers than for blastocyst-stage embryo transfers (by 102 g; P = 0.053).

Limitations, reasons for caution: A larger cohort size and longer-term follow-up are required to verify and further elucidate the impact of embryo culture methods on child health. Such studies will raise awareness regarding the sensitivity of *in vitro*-cultured human embryos to their environment, ultimately resulting in practices that decrease IVF risks to offspring.

Wider implications of the findings: Pregnancy outcome of the medium yielding fewer blastocysts was comparable or superior to that of other media, highlighting the importance of differentiating between the ability to support pre-implantation development versus the ability to yield viable embryos. Embryo culture medium had a greater impact than embryo transfer stage on live birthweight.

Trial registration number: UMIN000020910