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First randomized trial shows IVF culture media affect the outcomes of embryos and babies

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Fertility experts are calling on the companies who make the solutions in which embryos are cultured during in vitro fertilisation (IVF) to give a clear list of ingredients following publication of a trial that shows that the composition of these laboratory cultures affects the outcomes of the resulting embryos and babies.

The first randomised controlled trial (RCT) to look at the effect on perinatal outcomes of different IVF culture media found that they affected the numbers of viable embryos created, the rates of successful implantation in the womb, the pregnancy rates and the babies' birthweights.

The research is published today (Wednesday) in *Human Reproduction* [1], one of the world's leading reproductive medicine journals, together with a second paper [2] that reviews what is currently known about embryo culture media and which concludes "there is a strong case for demanding full transparency concerning the compositions of and scientific rationale behind the composition of embryo culture media". In an accompanying editorial [3], the journal's editor-in-chief, Professor Hans Evers, calls for urgent action by industry and regulators in the wake of these findings, saying that, just as with foods such as peanut butter, the exact composition of the culture media should be listed.

He writes that the results from the clinical trial show that "floating an

embryo for only a few days in a culture medium affects the birthweight of IVF children nine months later. The Barker hypothesis (Developmental Origins of Health and Disease) proposes that events in early life affect cardiovascular and metabolic health at an adult age. Small differences in birthweight may reflect more subtle disturbances that only will manifest themselves later in life. As of today, after publication of this RCT, not knowing the exact composition of their IVF culture media is no longer an option for clinical embryologists".

Dr John Dumoulin, the IVF laboratory director in the department of obstetrics and gynaecology at Maastricht University Medical Centre, The Netherlands, and his colleagues recruited 836 couples who were scheduled for IVF or ICSI (intracytoplasmic sperm injection) treatment at one of ten IVF centres in The Netherlands between July 2010 and May 2012. They randomised them to have their embryos cultured in one of two culture media: human tubal fluid (HTF) or G5. The randomisation was "double-blind" so that the patients, their gynaecologists, fertility doctors or outcome assessors did not know which medium was being used. Blinding of the embryologists was not possible as they performed the laboratory procedures. The researchers followed the progress of the couples for a year after randomisation or, in the cases where there were ongoing pregnancies, until birth.

A total of 383 babies were born alive, of which 300 were singletons and 80 were twin children. The researchers found that birthweight was lower in the G5 group compared with the HTF group, with an average difference of 158g. More singleton babies were born prematurely in the G5 group (8.6% versus 2.2%), and even when the researchers adjusted for gestational age at birth and gender, the average birthweight was still lower in the G5 group.

There was a greater number of embryos cultured in the G5 medium that were good enough to be implanted compared to those cultured in the

HTF medium (2.8 versus 2.3). In the G5 group implantation rates when using fresh embryos (rather than ones that had previously been frozen) were significantly higher (20.2% versus 15.3%) and pregnancy rates were significantly higher (47.7% versus 40.1%) than in the HTF group. There was a slightly higher (6%) live birth rate in couples assigned to G5 than those assigned to HTF (44% versus 38%), although this was not statistically significant.

Dr Dumoulin said: "For the first time, by means of a large randomised controlled trial, we have shown that human embryos that are cultured in vivo are sensitive to their environment and that something is programmed into these embryos during those few days before transfer to the womb that still has an effect nine months later. This being the case, we must be aware that David Barker hypothesised that the environment in early life, from foetus to the first two years of life, can have a significant effect on long-term health. This means that we should be careful and we should no longer blindly accept new culture media, or other alterations in laboratory or clinical procedures, without first rigorously studying effectiveness and safety."

However, he explained that his results are not as simple to interpret as saying that one medium was better than another, and that, for instance, the lower birthweight seen in the G5 group did not necessarily mean it was better or worse than HTF.

"It has already been shown that birthweight of children born to sub-fertile couples who were conceived naturally is lower than of children in the general population. There must be some patient-related factors in play resulting in a lower birthweight in these particular couples. So, perhaps in our study, the G5 babies are the 'normal' ones, with a birthweight that is correct for their particular origin from sub-fertile couples, while the HTF babies are too heavy. We just know too little at the moment."

One of the differences between the two culture media is that G5 medium contains certain amino acids that are not in the HTF medium. There are also about 20 other embryo culture media commercially available. Dr Dumoulin and his colleagues say that should be a greater level of scrutiny of them, with further randomised trials, that their full composition should be made publicly available by the companies that produce them and should have a scientific rationale; new formulations should only be introduced after properly conducted trials.

In the second paper, a working group of the European Society of Human Reproduction and Embryology, led by Professor Arne Sunde, head of obstetrics and gynaecology at the University Hospital in Trondheim, Norway, made the same recommendations. Their research showed that culture media vary widely, their composition is usually unknown by the end users (the embryologists, clinicians and patients), and data about the influence of the media on outcomes are conflicting.

Prof Sunde said: "The key issue is that we must know the composition of the culture media we use, since it seems to induce differences in the make-up of the children born. We have no information about long-term consequences of this, but we cannot rule out that the composition of the culture media may affect the health of children as they grow up and become adults."

At present, there is no uniform regulation of embryo culture media. In Europe, the majority of media approved for use carry the CE mark, but other non-CE media can still be used. In the USA media must obtain approval from the Food and Drug Administration before being marketed. Overall, fertility centres choose the media they want to use according to their own preferences. Manufacturers differ on whether and how they give information on the composition of the culture media and the scientific rationale. Usually they notify end users, such as embryologists, of any changes and the scientific data that support those

changes, but not always.

"It is not obligatory to declare changes and the information we might get is far from sufficient," said Prof Sunde. "We want to know in detail what changes have been made and the scientific basis for the changes, including animal and human clinical data backing the change."

More information: [1] "Influence of embryo culture medium (G5 and HTF) on pregnancy and perinatal outcome after IVF: a multicenter RCT," by Sander H.M. Kleijkers et al. *Human Reproduction* journal. DOI: 10.1093/humrep/dew156.

[2] "Time to take human embryo culture seriously", by Arne Sunde et al. *Human Reproduction* journal. DOI: 10.1093/humrep/dew157.

[3] "Peanut butter", by Hans Evers. *Human Reproduction* journal. DOI: 10.1093/humrep/dew129.

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