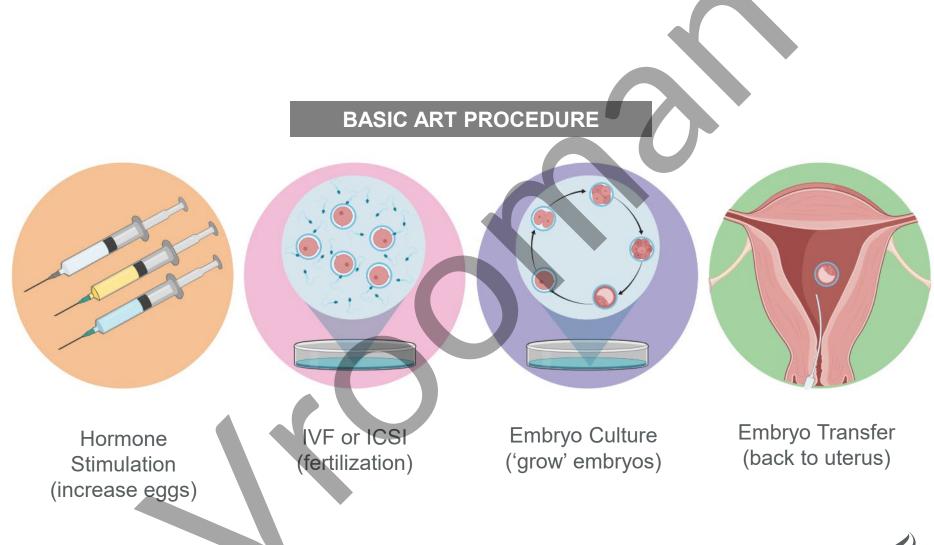


Optimizing embryo culture media to prevent adverse outcomes induced by Assisted Reproductive Technologies

Lisa Vrooman, PhD | August 9, 2023

Assisted Reproductive Technologies (ART)





Current ART usage

Over 9 million ART children born worldwide (ESHRE, 2020)

ART use has more than doubled in the last decade (CDC, 2023)

According to the CDC, in the US:

- ~ 450 ART clinics
- ~414,000 ART cycles/year (2021)
- ~167,000 were egg or embryo banking cycles
- ~97,000 ART children born/year
- 2.3% of all infants born are via ART

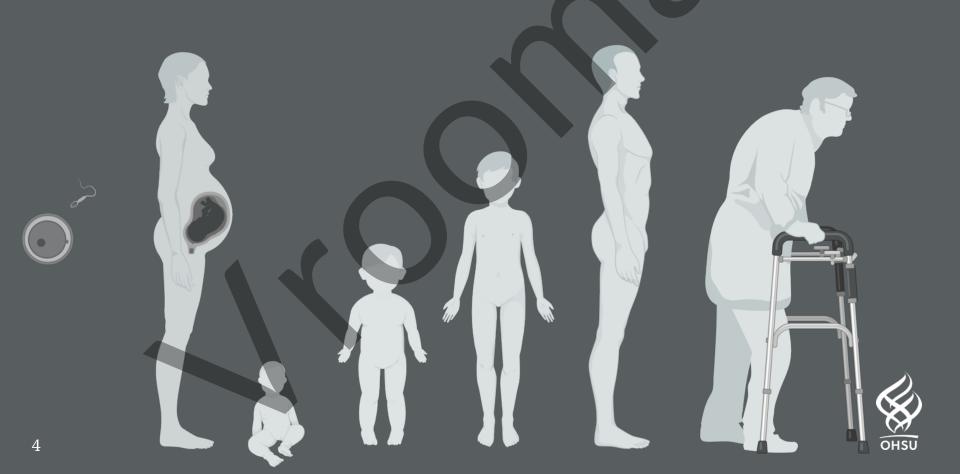






Developmental origin of health and disease (DOHaD)

- Research demonstrating the link between maternal, perinatal, and early childhood factors and risk on non-communicable diseases
- Are ARTs a critical window of 'exposure'?



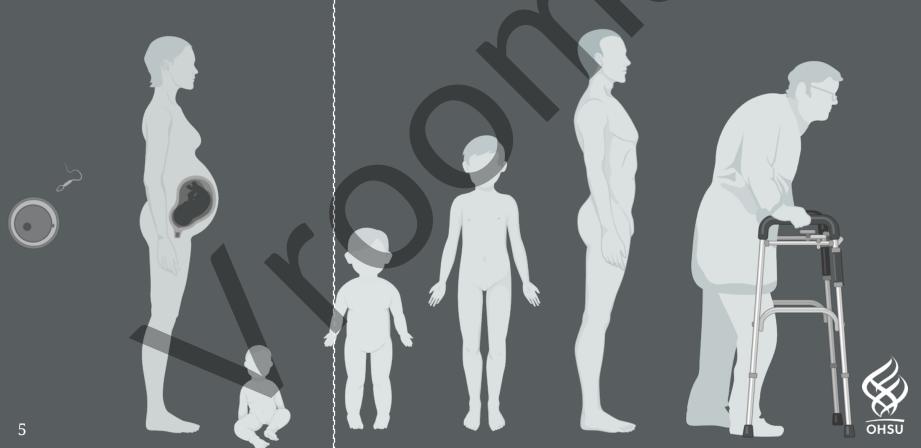
Developmental origin of health and disease (DOHaD)

SEVERE

MILD

- Infertility
- Pregnancy loss
- Congenital abnormalities

- Relatively normal postnatal development
- Risk for chronic diseases later in life.
- Directly affect fetus or indirectly affect fetus via placenta



What are the problems associated with ART?

Human ART pregnancies are associated with:

- miscarriage/stillbirth
- perinatal mortality
- imprinting disorders
- low and high birth weight
- abnormal placentation
- preterm birth
- preeclampsia

Animal Models of ART

- √ embryonic loss
- √ imprinting disorders
- ✓ low and high birth weight
- √ abnormal placentation



What are the problems associated with ART?

Postnatal outcomes in ART children:

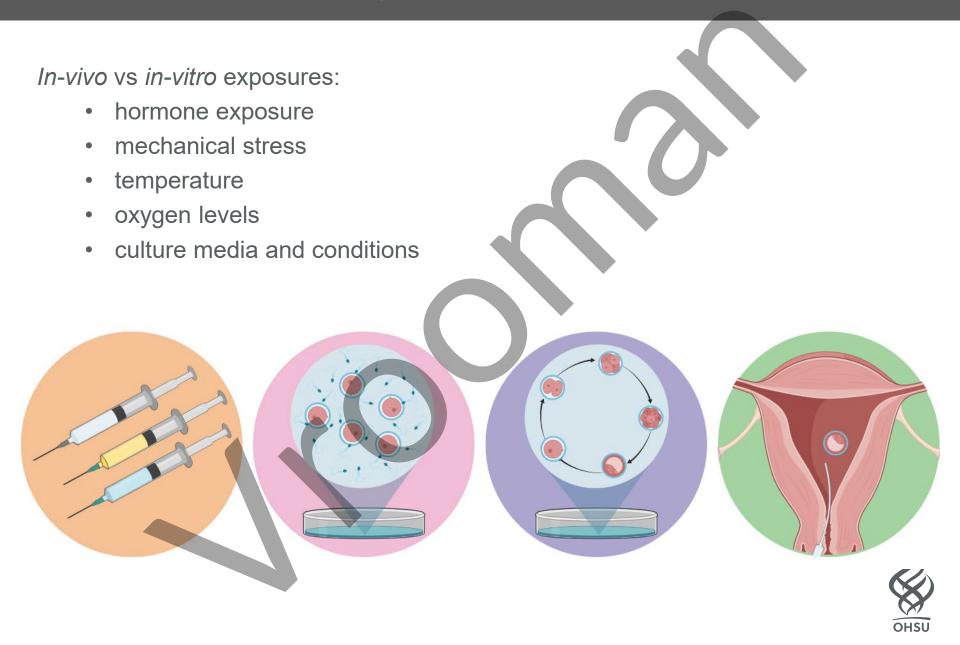
- increased blood pressure
- vascular differences
- increased adiposity
- hyperlipidemia
- impaired glucose homeostasis

Animal Models of ART

- √ increased blood pressure
- √ vascular differences
- √ increased adiposity
- √ hyperlipidemia
- √ impaired glucose homeostasis



What could be causing adverse effects?



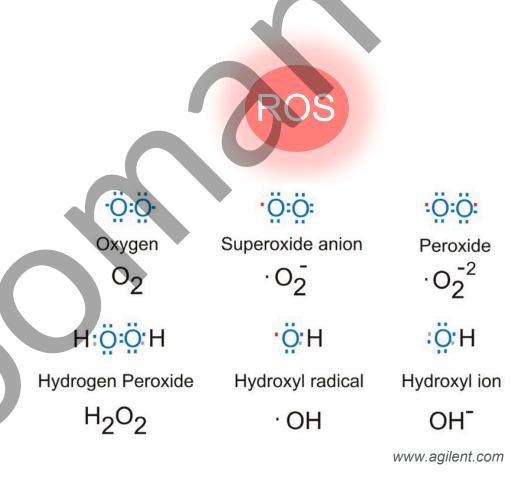
Reactive oxygen species

Reactive molecules derived from molecular oxygen

natural byproducts of cell respiration and enzyme reactions

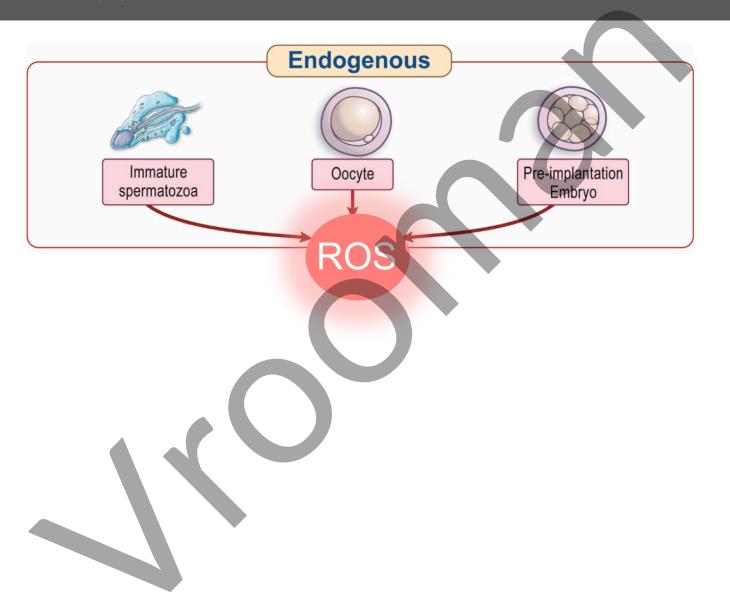
Too much, causes damage to:

- cellular lipids
- organelles
- DNA
- enzymes

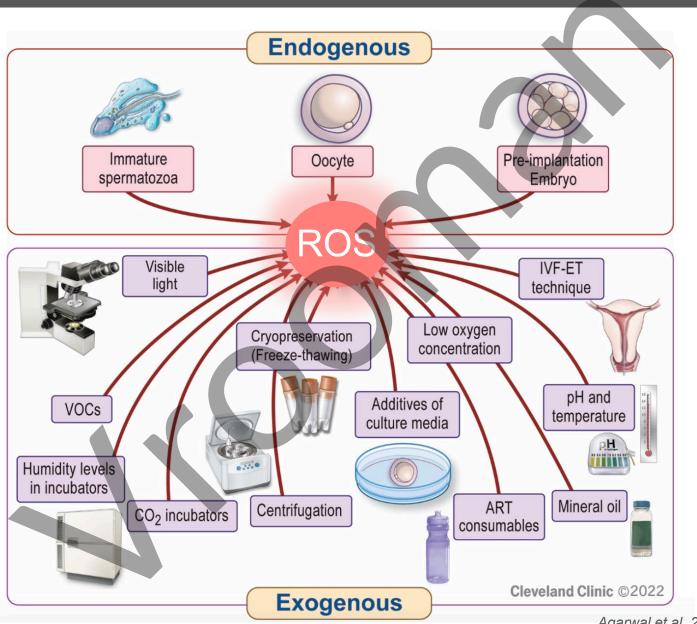




Reactive oxygen species



Reactive oxygen species





Can effects be prevented with antioxidant treatment?

Cells in the body normally deal with ROS with:

- enzymes
- antioxidant molecules

Several antioxidants have been tested for protective effects in embryo culture

- glutathione
- vitamin C
- acetyl-L-carnitine
- N-acetyl-L-cysteine
- alpha-lipoic acid
- melatonin





Can effects be prevented with antioxidant treatment?

CLINICAL TRIAL

Several studies have analyzed benefits of antioxidants on

preimplantation or perinatal outcomes

published: 13 May 2022 doi: 10.3389/fendo.2022.853999



Antioxidant supplementation overcomes the deleterious effects of maternal restraint stress-induced oxidative stress on mouse oocytes

Hua-Yu Lian, Yan Gao, Guang-Zhong Jiao, Ming-Ju Sun, Xiu-Fen Wu, Tian-Yang Wang, Hong Li and Jing-He Tan

Yong Zeng

ors have contributed

equally to this work

nan, a Prospective Clinical Trial.

* frontiers | Frontiers in Endocrinology

College of Animal Science and Veterinary Medicine, Shandons * Shandong Province, People's Republic -

Abstract

In this study, causing oxida Female mice exposure, mice caged with mal vivo by materr status, oxidative stress in mouse significantly in o development. Su glutathione synth injection of the ar postimplantation developmental pot injection overcame to increase the cha period in a human Reproduction (2013)

Melatonin Improves Quality of Repeated-Poor and Frozen-Thawed Embryos in Human, a Prospective Clinical Trial

Zhongjian Bao^{††}, Guangdong Li^{2†}, Rongxiang Wang^{2†}, Songguo Xue^{2*},





Exogenous L-Glutathione Improves Vitrification Outcomes in Murine Preimplantation Embryos

Nor-Shahida Abdul Rahman 1,20, Nor-Ashikin Mohamed Noor Khan 1,*0, Zolkapli Eshak 30,

hiah Abdullah 1,400,

ti Teknologi MARA,

00, Selangor, Malaysia

n Campus, Bandar Puncak

isted reproductive tech

ts in decreased viability

the preimplantation de-

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culture and vitrification

development Female

real injection of 10 IU of

horionic gonadotrophin

8 h after hCG to harvest

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1M GSH-supplemented

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r morphological quality

fied groups, there were

< 0.05). Similarly, in the

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ition embryo group. The

Human Reproduction, Vol.32, No.12 pp. 2404-2413, 2017

Advanced Access publication on November 10, 2017 doi:10.1093/humrep/dex33

OXIGINAL ARTICLE Embryology

Antioxidants improve IVF outcome and subsequent embryo development in the mouse

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Correspondence address: E-mail: david.gardner@unimelb.edu.au

Submitted on August 8, 2017; resubmitted on September 28, 2017; accepted on October 11, 2017

DY OUESTION: What is the effect of a combination of three antioxidants (Acetyl-L-Carnitine, N-Acetyl-L-Cysteine and α-Lippic ent in IVF medium during mouse oocyte and sperm collection, on fertilization and subsequent IVF embryo development?

MARY ANSWER: A combination of antioxidants resulted in faster developmental times from the 2-cell stage through to expanded st stage, accompanied by a significant increase in blastocyst cell number and a reduction of intracellular hydrogen peroxide (H2O2) levels. r is known already: The antioxidant combination Acetyl-L-Carnitine, N-Acetyl-L-Cysteine and α-Lipoic Acid, when present

abundance of Gpx1 and licability of GSH suppleels and the inhibition of

glutathione: vitrification

cryoprotectants, with e of preserving living e technique has been

com/journal/antioxidants



Introduction

Studies suggest detrimental effects et al. 1996. Csem Klonoff-Cohen et al. et al. 2006). Advers reproduction have et al. 1996, Peltonier 2008). Restraint of procedure develope (Paré & Glavin 1986 exposed to restraint impaired function pregnancy rates and Sugino et al. 1994, N

to Hobel & Culhane © 2013 Society for Reproduction ISSN 1470-1626 (paper) 1741-7

stage and embryo transfer, 31 patients were transplanted with 65 embryo including 24 MT embryo transfer, 41 non-MT embryo transfer. Cycle outcomes were compared between the two groups. Experiment II:A total of 143 supernumerary human cleavage-stage embryos (from non-respetated-poor-quality-embryo patients) vitrified on Day 3 after NVF were warmed and randomized into two groups: melatonin group (10 7 M melatorin added to the culture medium; n=71) and control group (n=72), and then cultured for 72 h. Rate of blastocyst and high-quality blastocyst, reactive oxygen species (ROS) levels of culture media as well as embryonic GPX1, CAT, Mn-SOD, Cu/Zn-SOD,

Reproduction a section of the journal Frontiers in Endocrinology Received: 13 January 2022 Accepted: 21 March 2022 Published: 13 May 2022 Bao Z, Li G, Wang R, Xue S, Zeng Y and Deng S (2022) Melatonin Improves Quality of Repeated-Poor and Frozen-Thawed Embryos in

Results: Experiment I: Results showed that the rate of Day 3 high-quality embryos (29.6% vs.19.5%) in the MT cycles group was significantly higher than that in the non-MT cycles group (P<0.05). The rate of available blastocysts (17.1% vs.12.7%) and clinical pregnancy rate (25.0% vs.17.1%) were in tendency higher in the group treated with melatonin (P>0.05). Experiment II. Results showed that the blastocyst rates in the melatonin administered group were significantly higher than in control group (42.25% vs.26.38%, P<0.05). There were no significant differences in high-quality blastocyst rates. In addition, quantitative PCR showed ression of CAT was significantly upregulated by melatonin treatment (P<0.05),

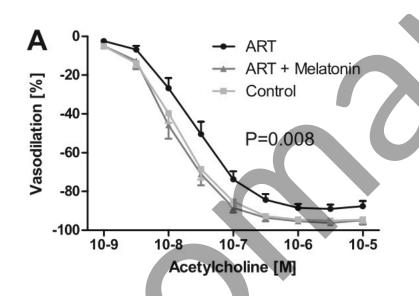
times to two cell cleavage (r < 0.01), which continued through to the expanded biastocyst stage (r < 0.03). Resultant biasto gnificant increase in both trophectoderm (TE) cell numbers, inner cell mass (ICM) and total cell numbers (P < 0.001). The adddants to IVF medium or embryo culture media exclusively also resulted in a significant increase in both blastocyst TE and ICM ng to an increase in total cell numbers (P < 0.001). Antioxidant supplementation of either oocyte IVF medium alone, or in both erm IVF medium, lead to significantly faster times to two cell cleavage, which continued through to the expanded blastocyst st cell number in both these groups had significantly higher TE cell numbers resulting in an increase in total cell numbers. In cone no differences in embryo developmental rates and blastocyst cell number when antioxidants were present only in the sperm vels of H_2O_2 were significantly reduced in pronucleate oocytes that were cultured in the presence of antioxidants (P < 0.001) introl, untreated embryos. Similarly, pronucleate oocytes treated with the combined antioxidants during pronucleate oocyte ed in significantly increased blastocyst ICM numbers compared with controls (P < 0.05).

, REASONS FOR CAUTION: Embryo development was only examined in the mouse.

CATIONS OF THE FINDINGS: These findings suggest that supplementation of antioxidants to the IVF medium, as well ure media, may further assist in maintaining the viability of human embryos in ART, conceivably through the reduction of oxi-

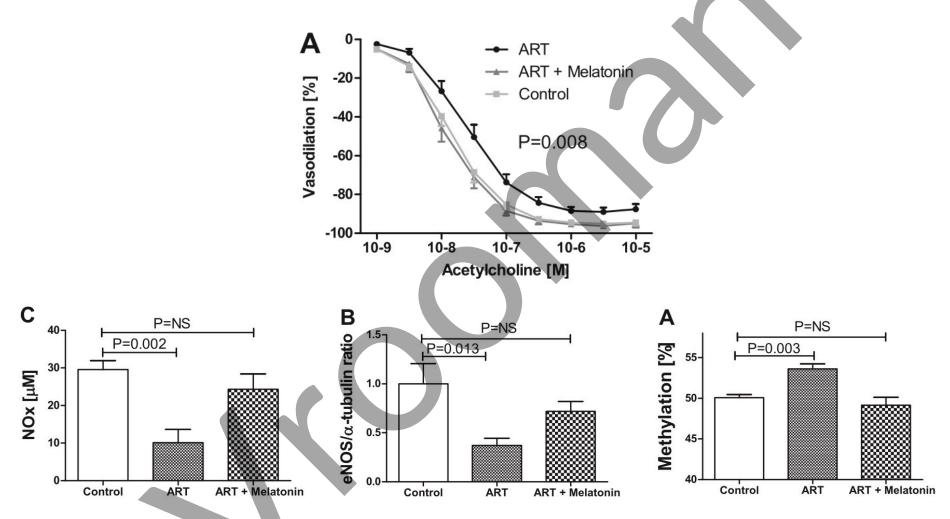
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Melatonin supplementation improves vascular outcomes

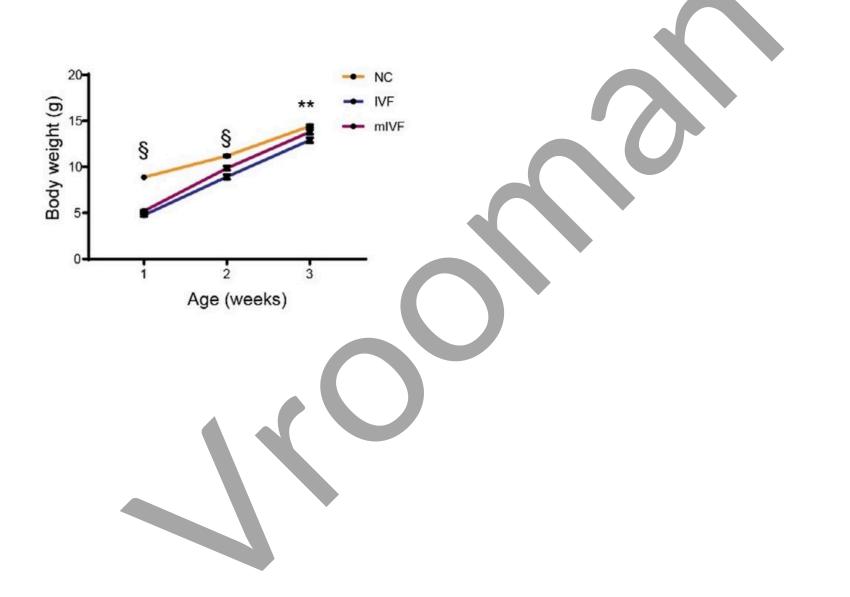


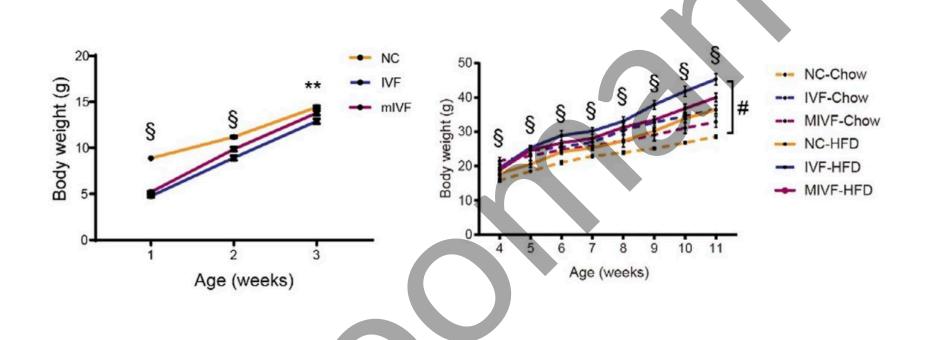


Melatonin supplementation improves vascular outcomes

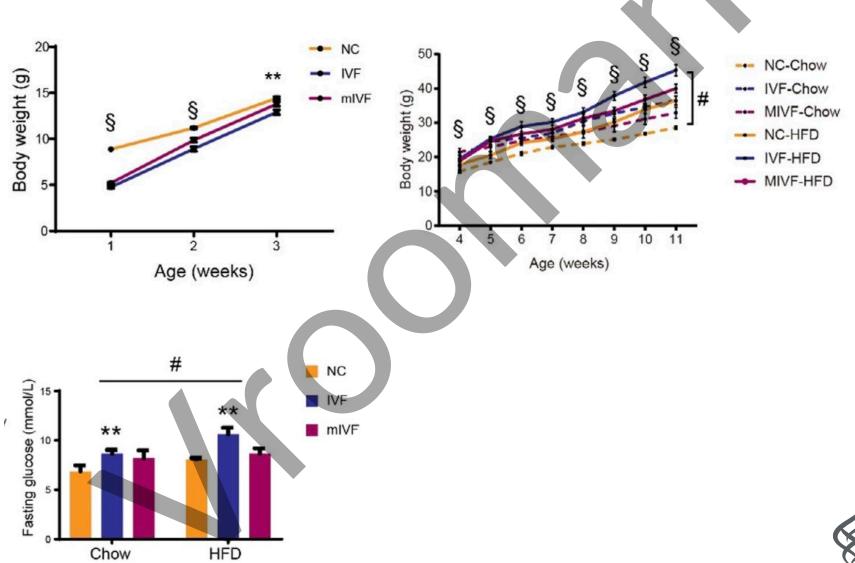


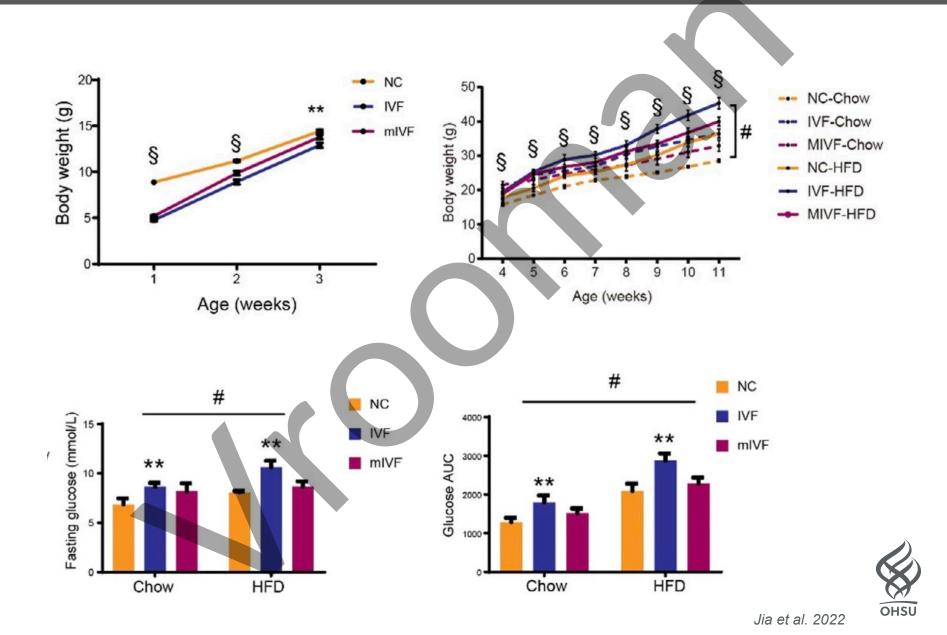








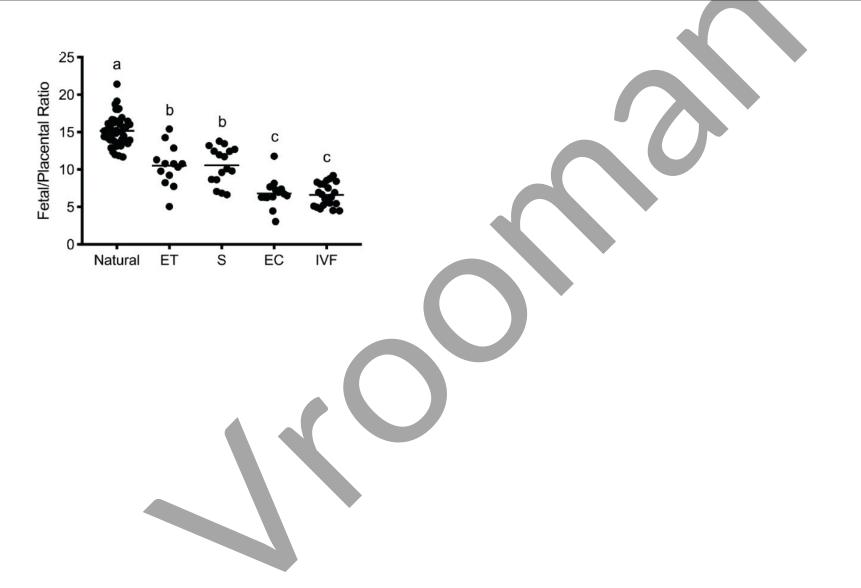


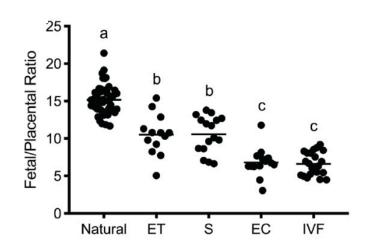


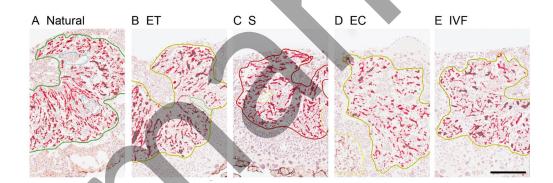
Postnatal cardiometabolic effect may be due to impaired placental development and function



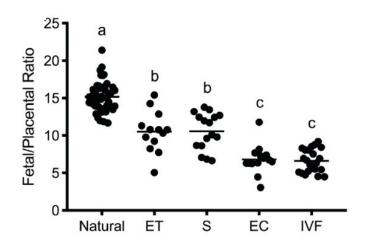


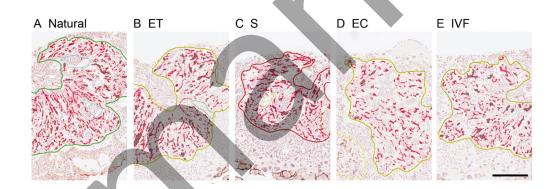


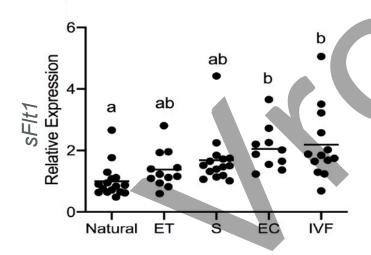




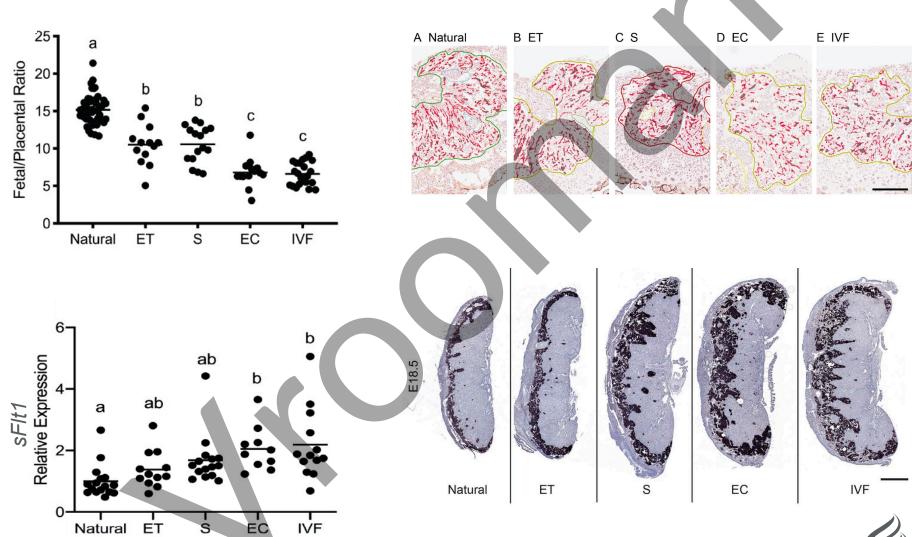


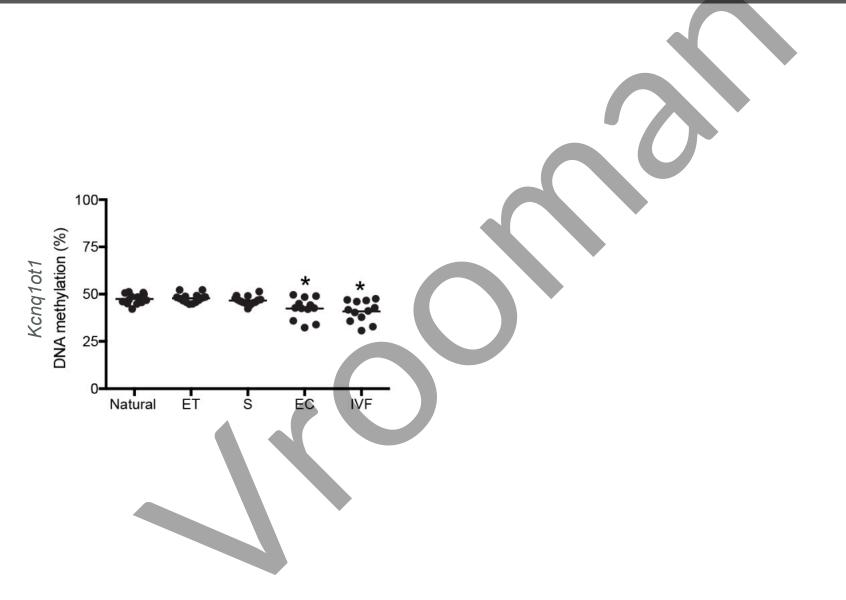




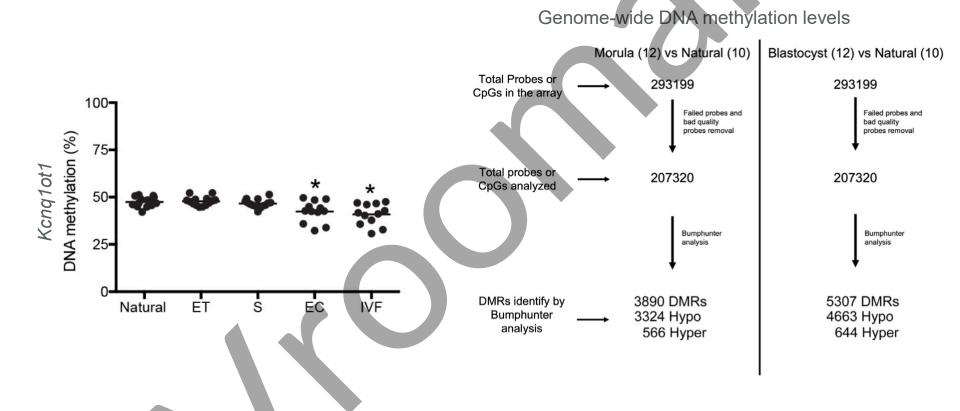






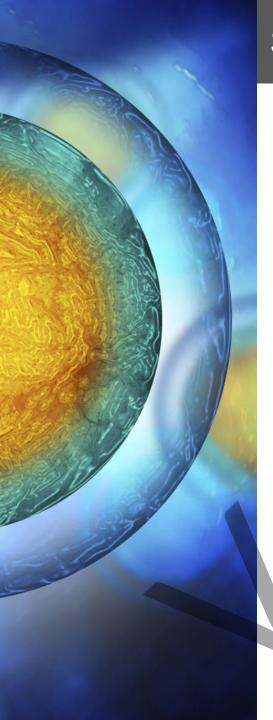












Summary

- ART is a widely used medical intervention that has the potential to cause pregnancy complications and adverse long-term health outcomes
- Reactive oxygen species impairing placentation might be a root cause of these adverse effects
- Culture media supplementation with antioxidants has shown potential benefits
- More research is needed to ensure culture additives are safe





Thank You