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Use of intrauterine human chorionic gonadotropin injection before embryo transfer

- a randomized control pilot study -

SUCCESSFUL IMPLANTATION

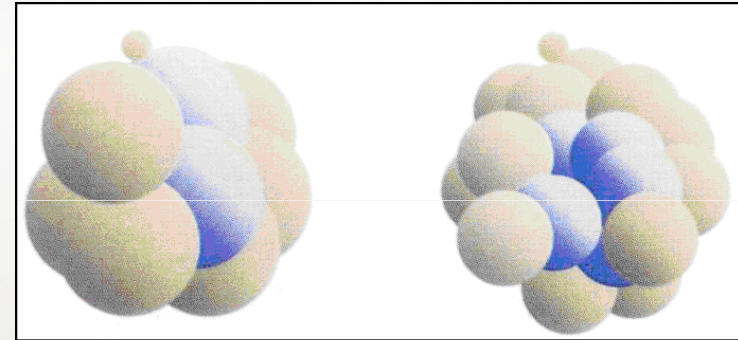
- Depends on various factors related to the embryo quality and the endometrial receptivity
- It is important that the embryo reaches the endometrial cavity during the period in which the endometrium is receptive, the “implantation window”



VIABLE EMBRYO

- Morphology
 - Subjective, static observation
- Blastocyst transfer
- PGS/Array-CGH
- Omics
 - Transcriptomics (Jones HR 2008)
 - Metabolomics (Brison HR 2004; Gardner HR 2011; Hardarson HR 2012)
 - Proteomics (Katz-Jaff FS 2006; Mains HR 2011)
- MorphoKinetics/Time-lapse
 - What your embryos are doing when you are not watching?

Look Good!
Here she comes!



ENDOMETRIUM

- Histology
 - Integrins (*Lessey FS 1994*)
- Genes
 - 14 genes identified correlated with RIF
- Tissue proteins
 - Stathmin 1 (*Domiguez HR 2009*)
- Secretion content
 - Proteomics of human endometrium
 - Endometrium fingerprint
 - Chemokines,
 - cytokines,
 - growth factors,
 - signaling factors,
 - prostaglandins,
 - lipids,
 - Nano-particles
- Embryo Interaction
 - Does the endometrium choose the embryo?
 - In Vitro Model (grow, decidualise, co-culture, observe)

(Malckon 2013)



ALTHOUGH RECENT ADVANCES....

- It is estimated that about 50% to 75% of lost pregnancies are due to failure of implantation
- The pregnancy rate remains around 30% per cycle



WHAT WE KNOW

- Implantation is a very intricate process that is regulated by many factors, the most important of which is human chorionic gonadotropin (hCG)
- hCG is one of the early embryonic signals and is secreted by the embryo before its implantation



Paracrine role of hCG

- Increases the capacity of apical cell adhesion
- Regulates proliferation of myometrial smooth muscle cells
- Reduces cell contractility
- Increases progesterone receptors
- Regulates the development of local immune tolerance
- Initiates endometrial angiogenesis at the implantation site
- Initiates and controls invasion for the establishment of hemochorial placentation



Direct effect of hCG

Intrauterine injection 500 IU of hCG/mL

- provoked a significant inhibition of intrauterine insulin-like growth factor-binding protein 1 (IGFBP-1) and macrophage colonystimulating factor (M-CSF)
- Significantly stimulated leukemia inhibitory factor (LIF), vascular endothelial growth factor (VEGF), and matrix metalloproteinase 9 (MMP-9)

Licht et al, 1998



STUDY QUESTION

- Does the administration of intrauterine human chorionic gonadotropin injection (hCG) before embryo transfer improves outcomes in IVF?



STUDY DESIGN, SIZE, DURATION

Randomized control pilot study

Between July 2012- September 2013

Randomization was performed in a 1:1 fashion to one of two groups: with or without hCG intrauterine injection

Adequate allocation concealment was assured from sequentially numbered, opaque, sealed envelopes prepared from a computer-generated list



PARTICIPANTS & SETTING

A total of 194 IVF women all >40 years old receiving donor eggs were recruited

Patients were stratified for 0, 1-2 and >3 previous failed donor-cycles

hCG was administered intrauterine before embryo transfer

Data analysis: Fischer's exact test (GraphPad Prism).



LIMITATIONS

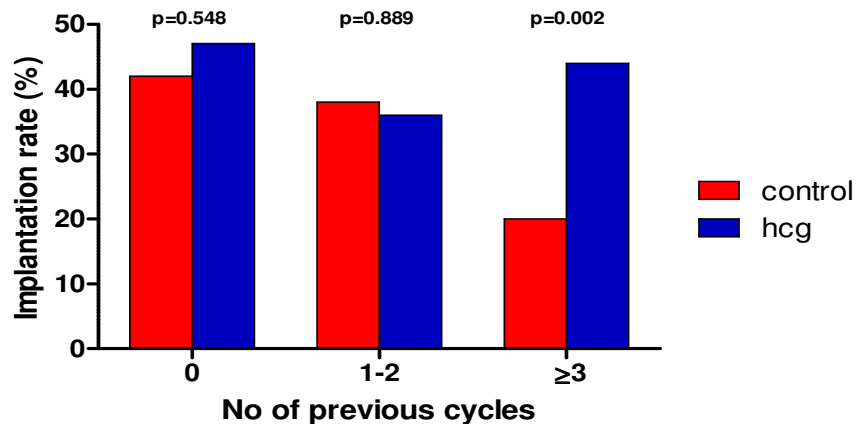
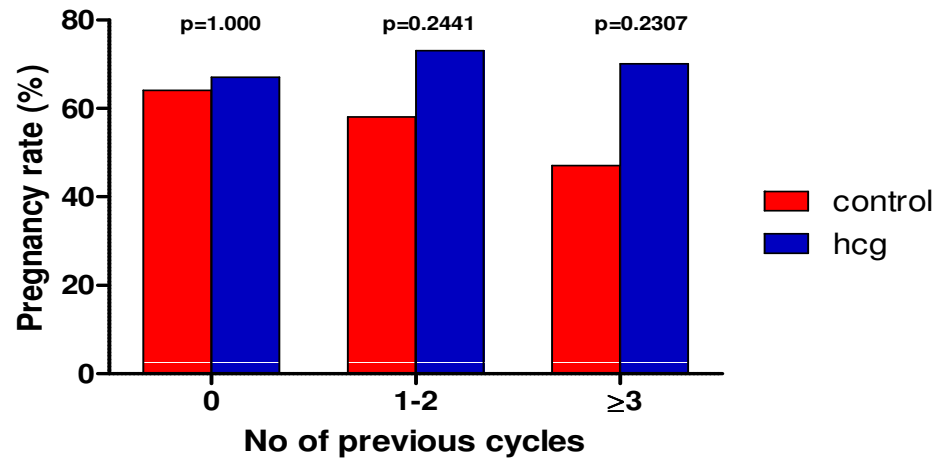
Our pilot study involves a limited sample size in order to evaluate the preliminary data before conducting a larger trial

Selection bias was controlled by randomization

Blinding of patients was not possible in this study, but since the outcome (pregnancy) is robust, blinding would have been unlikely to affect the results



MAIN RESULTS



In hCG patients, IR was found statistically significant in patients with previous multiple failed donor attempts

hCG IR: 44% P=0.023 versus Control group IR=20%)



CONCLUSION

This pilot study indicates an increase in the probability of achieving pregnancy and an increase on implantation rates after administration of intrauterine hCG, for women >40 years old with multiple previous failed IVF cycles following IVF program with donor eggs



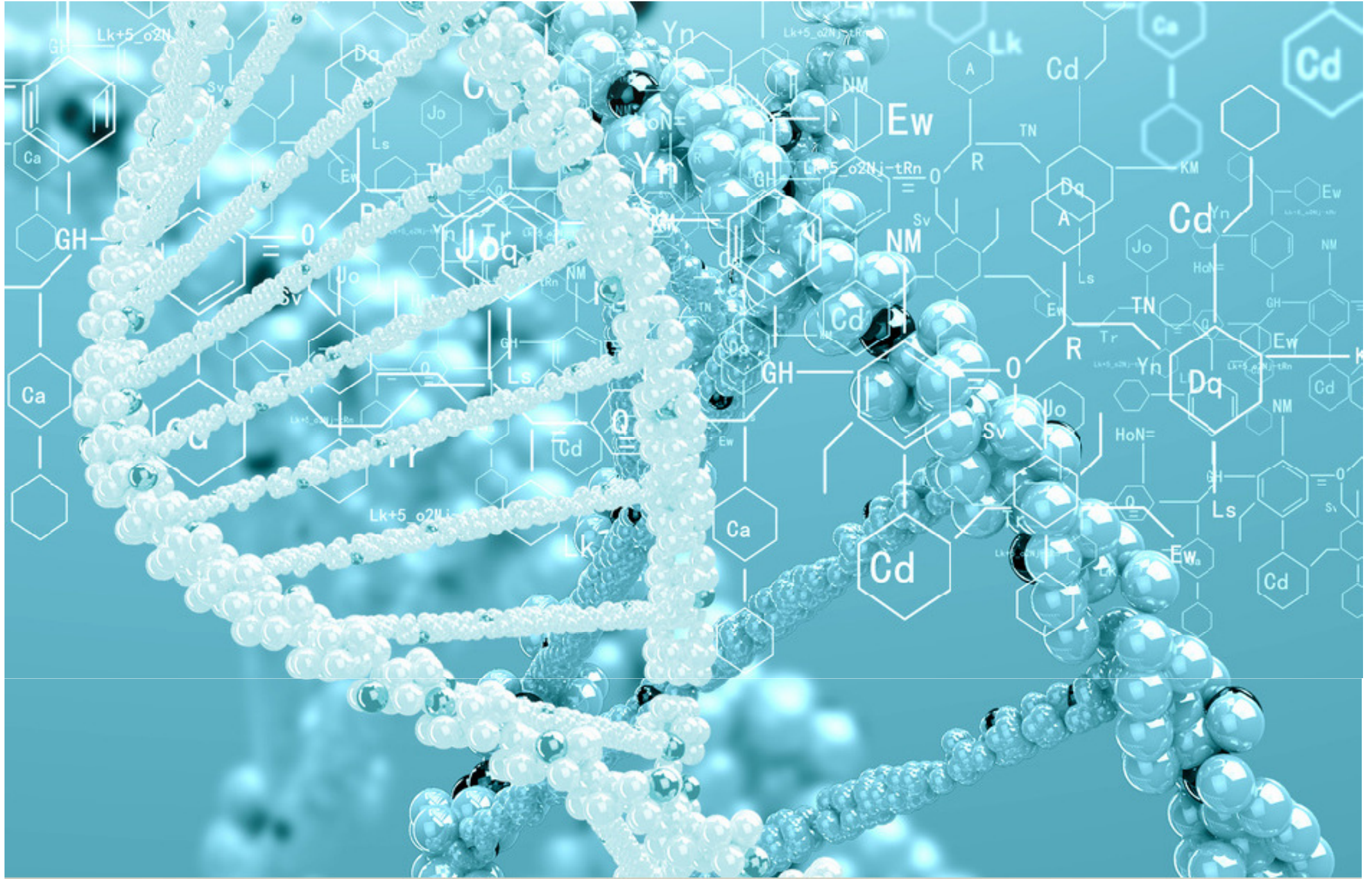
WIDER IMPLICATIONS OF THE FINDINGS

Positive effect following the administration of intrauterine hCG injection before embryo transfer

A larger RCT will assess, with more confidence, the effect of hCG on the probability of pregnancy

STUDY FUNDING/ COMPETING INTEREST(S): None. Not competing interests.





Thank you!

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