HUMAN SPERM "CYCLE" BETWEEN STATES OF FERTILITY AND INFERTILITY, THE KNOWLEDGE OF WHICH CAN PREDICT SUCCESS IN ICSI

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BACKGROUND

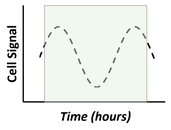
For fertilization to occur, sperm must reach functional maturity; sometimes referred to as undergoing the process of capacitation. Prior preliminary research suggests that functional maturation of ejaculated sperm occurs in sequential waves and synchronization of sperm within these waves may impact the success of fertilization during IUI or IVF procedures [1]. An assay to detect molecular changes to sperm during this maturation as a means to improve timing of sperm use to coincide with improved sperm functionality has been developed. How this functional sperm assay may impact outcomes with use during ICSI is unknown.

OBJECTIVE

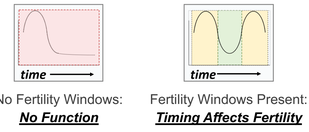
To determine if timing of sperm use to coincide with maturational waves detected via a functional assay impacts success rates following ICSI.

Discovery: The 4 Factors of The Male Fertility Cycle

1. Periodic Fertility Windows Called "Cycling"



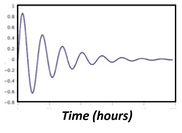
2. Cycling & Timing Determines Fertility State



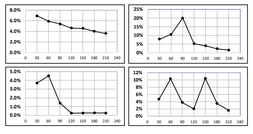
No Fertility Windows: ***No Function***

Fertility Windows Present: ***Timing Affects Fertility***

3. Cycling Fades with Time -- and Fertility With it



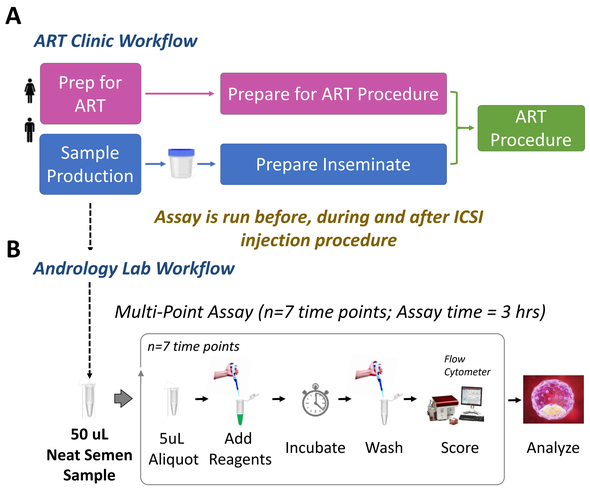
4. Each Ejaculate is Different



The Male Fertility Cycle discovery is grounded in 4 key observations: (1) Sequentially-maturing groups of sperm in a single ejaculate exhibit specific functional changes that indicate fertility. (2) The presence and timing of these functional changes in sequential groups of sperm in the ejaculate determine its fertility. Ejaculates without these changes are non-functional. (3) These changes, and therefore the ability to fertilize, dissipate with time. (4) Each ejaculate is unique.

MATERIALS AND METHODS

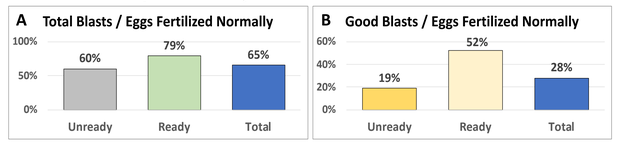
This was a prospective double-blind pilot study. A functional sperm assay (Arex Assay), which detects levels of a novel receptor level (FcR) was performed on sperm samples used during routine ICSI cycles (n=49). The assay determines mature versus immature sperm based on a number of FcR expression levels. Briefly, 5uL aliquots of semen were analyzed at 30-min intervals to determine the proportion of sperm that were expressing FcR and the temporal changes in FcR expression levels were analyzed. Semen samples were categorized according to gamete fertilizing readiness depending on FcR expression patterns. ICSI was performed as usual, and knowledge of the functional assay was not used to alter timing. The fertilization rate and production of Day 5 good quality blastocysts (>3BB) were evaluated. Outcomes were then stratified and compared via the expression levels of FcR from the functional assay to determine if any correlation existed.



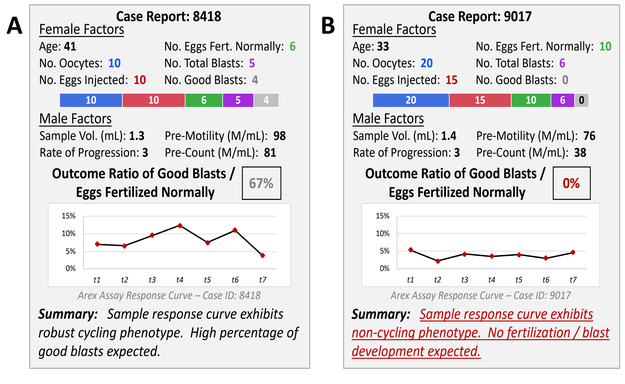
(A) Couples presenting for ICSI at the clinic are prepared for their respective procedures. The male produces a semen sample from which 50 uL of neat semen is apportioned for analysis with the Arex Assay. (B) Aliquots from a neat semen sample are removed at defined intervals for assay using flow cytometry to identify positively and negatively labeled sperm across time.

RESULTS

Among the ICSI cycles performed, the fertilization rate from cycles using mature (ready) sperm did not differ from cycles using immature (unready) sperm (76.5% % vs. 77.7%, respectively). **However, the number of good quality blastocysts increased when using ready sperm compared to unready sperm as defined by the Arex Assay.** ICSI cycles using ready sperm produced 53/101 (**52%**) good blasts; ICSI cycles using unready sperm produced 53/278 (**19%**) good blasts. **Aneuploidy rates were unaffected.** The odds ratio for reproductive outcome among ready vs unready sperm was 4.69 (95% CI: 2.78, 7.89; p<0.0001; Fisher's exact test). There were smaller differences in the percentage of total blasts produced by ready or unready male gametes. Blastocyst production as a function of male gamete readiness is shown as ratios of eggs fertilized normally for (A) total blasts, and (B) good blasts, respectively.



Case reports (A) and (B) illustrate the assay's ability to identify phenotypic fertility function in clinical semen samples that impact ART outcome. The presence of "normal" semen parameters and adequate female-side retrieval values are not sufficient for good blast formation when sperm function is deficient per Arex Assay.



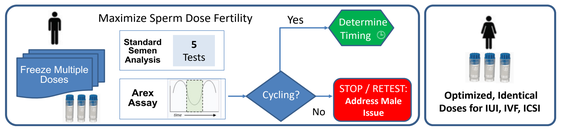
CONCLUSIONS

In this pilot study, ICSI procedures yielded more high-quality day 5 blastocysts when sperm were in the "ready" or mature state compared to those in the non-ready state. This suggests that, like other procedures during ART, timing of gamete use may impact outcomes. While oocyte quality was not controlled using split samples in this study, future studies will control this variable.

Summary

1. **In this double-blind ICSI study, the number of good blastocysts produced differed depending on male gamete readiness.**
2. Ejaculated sperm mature in sequential waves to gain fertility potential.
3. Presence and timing of sperm maturation waves determine fertility potential.
4. Every ejaculate is different.
5. Sperm maturation wave production dissipates over time after ejaculation.
6. Aneuploidy (PGT-A) rates of blastocysts were not affected between ready and unready sperm.

Potential to Enable Functionally-Ready ART Doses



A semen sample is aliquoted and cryopreserved to create functionally identical ART doses. Optimal insemination timing and functional characteristics are determined from the Arex Assay. Assay results along with accompanying semen analysis data provide clinical direction.

REFERENCES

1. Librach et al., Human Sperm "Cycle" Between States of Fertility and Infertility, the Knowledge of Which Can Predict IUI Success. American Society of Andrology May 7-10, 2022; La Jolla, CA..

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