Is the Immune System (Autoimmunity and Inflammation) Really Irrelevant to IVF Success as Suggested by Some?

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Conflict Statement

Dr. Gleicher is listed as co-inventor on a number of pending patent applications claiming diagnostic and therapeutic benefits from determination of CGG repeat numbers and ovarian *FMR1* genotypes and sub-genotypes.

Dr. Gleicher is co-inventor of awarded U.S. patents, claiming therapeutic benefits for supplementation of DHEA in women with diminished ovarian reserve, a topic discussed in this talk. Other patent applications in regards to DHEA and other fertility-related claims, with no relationship to this talk, are pending. Dr. Gleicher receives royalties from, and owns shares in Fertility Neutraceuticals, LLC, a distributor of a DHEA product.

Dr. Gleicher is co-inventor of three pending patent applications claiming potential therapeutic benefit for anti-Müllerian hormone (AMH) in infertile women. Dr. Gleicher owns shares in OvaNova Laboratories, LLC.

Outline

- History of reproductive immunology
- Autoimmunity and reproductive failure
- How we went wrong!
- The paternal semi-allograft
- Developing tolerance
- Effects of hyperactive immune systems on developing tolerance
- Evidence for tolerance-inducing pathways

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History

- 1950s: Medawar & Billingham
- 1979: ASRI
- 1981: Lubbe et al, Miscarriage association with LA
- 1983: Gleicher & Friberg, Association with autoimmunity in general
- 1994: Geva et al, Association with implantation failure

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- Exaggerated claims
- Industry pressure
- “Everything autoimmune”

Backlash!

Hill and Scott, Immunologic tests and IVF: “Please, enough already.” Fertil Steril 2000;74:439-42

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The big pregnancy puzzle

- The embryo/fetus is a semi-allograft
- It, therefore, should be rejected by a normally functioning immune system
- Yet, a normally functioning maternal immune system does not reject the implanting embryo
- WHY???

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Tolerance

- A normally functioning female immune system allows implantation and maintains pregnancy by developing tolerance
- Reprograms itself from rejection to tolerance
- And does so not by becoming insufficient but by inducing tolerance pathways
- Tolerance is time-limited

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Hyperactive immune systems often lack the ability to reprogram themselves

- Autoimmunity
- Inflammatory conditions
- Hyper-allergenic women

Hyperactive immune systems

↓

Inadequate tolerance induction

↓

Allo-immune response

↙ ↘

Implantation failure Miscarriage

Women with poor tolerance induction early in pregnancy usually also demonstrate early termination of pregnancy

- Pre-eclampsia/eclampsia
- Premature labor
- Other late pregnancy complications

The problem is

allo-immunity

and not

autoimmunity

The cause is

poor tolerance

and not

autoimmunity

- Therefore, searching for individual markers of autoimmunity or inflammation makes no sense
- Suspicion should arise when women have historical or laboratory evidence of a hyperactive immune system

Tolerance pathways

- Th1 ⟶ Th2 responses
- Helmiths (*Blackwell et al, Science 2015*)
- Influenza vaccine (*Sheffield et al 2012; Brattou et al 2015; War?? Et al 2015; Oli??? Et al 2016; Neagou et al 2016*)

The future

- Correct diagnosis of insufficient tolerance
- Therapeutic suppression of allo- (not auto-) immune responses
- Therapeutic boosting of tolerance pathways

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