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Review

Cross talk during the periconception period

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A B S T R A C T

The cross talk between gametes, embryos, and female reproductive tract plays a crucial role in fine tuning of different reproductive events as well as influencing the epigenetic profile of offspring and their health in adulthood. Here, we describe some background to the recent investigations leading to the discovery of this cross talk. We will also point to important requirements for understanding the maternal communication with gametes and embryos. Finally, we mention two probable hypotheses regarding how gametes and embryos are recognized by the female reproductive tract. It is clear that understanding this cross talk is leading to the production of new means for increasing fertility and potentials for affecting the epigenomic profile of an individual.

1. The fall and the rise of research on cross talk during the periconception period

Transport of the gametes, the final gamete maturation process, fertilization, early embryonic development, and embryo implantation take place in the oviduct and/or fallopian tubes and the uterus and/or uterine horns. These are all very important events that occur during the periconception period, leading to creation of new offspring. However, our knowledge of the periconception environment and how it is regulated is very limited. In the last 40 years, the support for research in this field has been limited. Neglecting this area of reproductive research has not only been due to a lack of funding opportunities and limited financial support from the funders; the negligence has also originated from the scientific community. The dominant view in the scientific community has been rather dismissive of the importance of the periconception milieu and the important role that it may play in regulating important reproductive events. This attitude, at least for the last 3 decades of the 20th century, was the dominant view in the scientific community even going as far as rejecting grant applications on the basis of the lack of importance in researching this area of reproductive sciences. One of the authors of the present article (Alireza Fazeli), once had a research grant application rejected because of a reviewer's comment, stating that the topic of investigation–the periconception environment–is "interesting" but not "important".

Probably the origins of this view–dismissing the importance of the periconception milieu–partially resulted from the success of IVF and other assisted reproductive technologies. The successful establishment of IVF as the method of choice for infertility treatment was not just a huge advance in helping infertility patients but was a turning point for our understanding of the events taking place during the periconception period. *In vitro* fertilization allowed detailed investigation of different events that take place in the maternal tract. Indeed, IVF contributed substantially to research findings in our field. However, at the same time it supported the view that the milieu of the oviduct and/or fallopian tube and the upper parts of the female reproductive tract is replaceable by a simple combination of buffered salts called "IVF culture media". Hence, from the mid-1970s, the leading view gaining support between experts was that the oviduct and/or fallopian tubes, and generally the upper parts of the female reproductive tract (that are the exact location and/or host of

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periconception events), are just passive contributors toward the events taking place during the periconception period. Their only function was regarded as providing a milieu with the right temperature, pH, and nutrients but without involvement and/or contribution in the fine tuning and regulation of different events taking place during this period.

This was the dominant view in the field until around the beginning of the 21st century that several lines of evidence started to challenge this dogma. Better understanding of how events such as “sperm storage” in the female reproductive tract are mediated or the discovery of phenomena such as “large offspring syndrome” attracted the attention of scientists to the importance of the periconception milieu and the role that the periconception milieu plays in regulating fertility as well as the future health and development of offspring. Discovery of the sperm storage mechanisms, and the fact that most of internally fertilizing species are able to preserve sperm viability, not only by providing nutrients for spermatozoa, but by influencing diverse functional regulatory processes such as sperm plasma membrane fluidity, pointed to the presence of active sperm regulatory processes in the oviduct [1–4]. In cattle and sheep, embryos exposed to *in vitro* culture environments before the blastocyst stage had resulted in the development of unusually large offspring (large offspring syndrome) that also exhibited a number of organ defects [5]. The cause of large offspring syndrome was blamed on the presence of the serum in the *in vitro* culture media [6]. These interesting observations and the fact that these small changes in in vitro conditions can have such profound effects in the fate of the offspring, in addition to advances made in the field of epigenetics, attracted a lot of attention toward understanding how changes in the periconception milieu can affect the future health of the offspring, as well as how the periconception milieu is regulated and organized.

2. Difficulties in the discovery of cross-talk mechanisms during the periconception period

Early work on deciphering communication between the maternal tract, gametes, and embryos was mainly focused on understanding the effect that the maternal tract components had on gametes or embryos. Most of research in this field was driven by application and commercial interest to understand what molecules or components of the tract are responsible for improving the preservation of sperm, supporting the maturation of oocyte and/or help with the development of embryos.

Seldom in the literature, was there a report, aimed at understanding whether the interactions between the maternal tract, gametes, and embryos were truly cross talks between the female reproductive tract from one side and gametes or embryos from the other side. Moreover, it was not clear whether the cross talk was directed from gametes and embryos toward the female reproductive tract too. Part of the reason for this negligence may have been caused by a lack of a commercial interest or a practical application to drive the research in this field. For example, the discovery of molecules responsible for the maintenance of sperm viability in the female reproductive tract, and their use in commercial diluents for semen preservation, or finding the factors that promote the *in vitro* development of embryo to help infertile couples, were attracting big commercial interests and fueling further research in understanding what is produced by the maternal tract in support of gametes or embryo function. However, at the same time, the main driver of research and discovery of the changes in the maternal tract responses to spermatozoa, or embryo was pure basic scientific interest.

The other hindrance in research to understand the responses of the female reproductive tract to gametes and embryos was unavailability of an, easy to measure, so called “end point of assay” for evaluating the oviduct and/or fallopian tube responses to gametes and embryo.

For example, in the case of measuring the sperm responses to oviductal factors, scientists were able to use viability or general andrology routine tests such as measuring the percentage of motile spermatozoa to check whether different components of oviductal fluid had any effects on sperm function. In the case of oocytes, several tests existed to check the effect of oviduct and/or fallopian tubes on the maturational stages of oocytes, i.e., nuclear or cytoplasmic maturation or even zona pellucida hardening [7]. Even in the case of embryos, simple microscopy was enough to measure the rate of growth and development of an embryo. However, such proper and relatively easy to measure end points of assay were not available to the scientists investigating the maternal responses to gametes and embryo until the latter years of the previous century.

The other major issue that had stalled investigation in this field was the subtlety of the reactions of the female reproductive tract to gametes and embryos. Today we know that changes happening in the maternal tract, e.g., at the transcriptomic level, in response to gametes and embryos are in minute amounts. Hence, it is very important to employ technologies that have a holistic ability and can detect the relatively fine changes between large and diverse populations of transcripts. Maternal responses to gametes and embryos are not major physiological events that produce huge transcriptomic or proteomic changes in the tissues and organs involved. They produce subtle modifications, and detecting these changes needs careful experimental design and/or planning as well as avoiding the background noise levels that can mask or hinder the detection of these reactions. Potential factors that may cause vast physiological transcriptomic and proteomic alterations in the female reproductive tract milieu, e.g., changes in the reproductive tract milieu due to sex hormone alterations in the reproductive cycle, can themselves substantially alter the genome or proteome of the female reproductive tract and completely hide the minute responses of the female reproductive tract due to the arrival of gametes or embryos in the tract [8]. Hence, a need exists to try to differentiate and recognize the fine responses of the maternal tract to gametes and embryo from the background noise.

Finally, another major improvement, particularly in the *in vivo* analysis of periconception cross talk between gametes and embryos has been the application of *in vivo* models that provide both the test and the control within one female to check for the responses of the female