The relationship between recurrent pregnancy loss and the male contribution

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Judge a man by his questions rather than his answers.

—Voltaire

Sometimes one looks to the past 50 years in the field of reproductive medicine with veneration and recognition of truly amazing scientific progress. Other times, however, one must humbly acknowledge that despite the remarkable innovations over these years, there are still open questions. In the May 1966 issue of *Fertility and Sterility*, there was an article by C.A. Joel titled, "New etiologic aspects of habitual abortion and infertility, with special reference to the male factor" (1). An article in the January 2016 issue of *Fertility and Sterility* examined the same idea: the relationship between recurrent pregnancy loss and sperm characteristics (2). Despite the improvements and advances in the field, 50 years later, this relationship has yet to be expounded.

Recurrent pregnancy loss is defined as two or more consecutive pregnancy losses in the first or early second trimester. Most of research in this area has focused on maternal factors such as meiotic error, oocyte quality, obesity, uterine architecture, metabolic factors, infection and immunology. The male contribution has been largely unexamined and remains poorly understood.

Preimplantation genetic screening (PGS) may improve in vitro fertilization live-birth rates by increasing embryonic implantation and reducing spontaneous abortions. Given the male provides 50% of the DNA to the developing embryo; it is not surprising that paternal factors have been hypothesized to be a culprit in pregnancy loss. However, PGS has demonstrated the majority of aneuploidies are derived from the oocyte. What then, could be the etiologies and mechanisms by which paternal factors impact pregnancy loss?

In the era prior to sophisticated DNA screening, tools like microspectrophotometry and microscopy were used to examine semen. In the 1966 article by Joel (1), an association was noted between diminished DNA content in sperm, oligospermia, and spontaneous abortion. The biologic mechanism by which these factors led to miscarriage was unclear. Fifty years later, despite better methodologies for DNA assessment such as the terminal deoxynucleotidyl transferase dUTP nick end labeling test, fluorescence in situ hybridization for sperm aneuploidy screening, and evaluation of sperm chromatin, a similar observation was reported, with no better understanding of why? A higher percentage of men who had recurrent spontaneous abortions had evidence of DNA damage in sperm compared to men who had a recent live birth and no history of recurrent miscarriage. Despite 50 years of innovation and progress, we are

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no closer to understanding the mechanism of the male contribution to pregnancy loss.

As new technologies continue to emerge, perhaps these questions will be answered. We hope for continued progress over this next half century so that this same column in the 2066 issue of *Fertility and Sterility* will bear answers to today's questions.

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