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EDITORIAL

Sperm DNA fragmentation in miscarriage – a promising diagnostic, or a test too far?

The scientific basis for diagnostic testing for sperm DNA fragmentation (SDF) is a topic that seems to return frequently for debate and discussion (Lewis, 2015; Drobnis and Johnson, 2015). The essential question is: does SDF analysis add useful additional information – beyond that obtained from basic semen analysis – sufficient to change patient diagnosis, therapy and/or understanding of prognosis? Currently for subfertility, the guideline answer is no (Barratt et al., 2010; Practice Committee of the American Society for Reproductive Medicine, 2013).

Recurrent pregnancy loss (RPL) is generally viewed as a condition distinct from sporadic miscarriages. It is estimated that 5% of women experience two consecutive miscarriages, and approximately 1% suffer three or more consecutive miscarriages (Rai and Regan, 2006; Practice Committee of the American Society for Reproductive Medicine, 2012). The answer to the question of whether some of the unexplained cases could be due to the quality of the sperm DNA and/or its packaging is proving enigmatic.

There are two main problems with current SDF studies. First, there are 4 main techniques for assaying SDF or chromatin properties, which actually assay quite different parameters: single cell gel electrophoresis assay (SCGE, also known as Comet), sperm chromatin structure assay (SCSA), TdT-mediated dUDP nick-end labelling (TUNEL) and sperm chromatin dispersion (often known as HALO). Each of these tests may individually be measuring something that does or does not provide prognostic value – though all are interrelated to a greater or lesser extent via properties of the DNA – but what is certain is that they do not measure exactly the same thing. These assays are also interrelated to protamine deficiency via effects on chromatin structure (Ni et al., 2016), adding further complexity to the repertoire of related tests.

DNA becomes fragmented for a number of reasons, for example abortive apoptosis (programmed cell death) (Sakkas et al., 2003), environmental exposure to toxins, fever, or defects in packaging (Aitken et al., 2014). An advantage of SDF testing in idiopathic recurrent pregnancy loss is that usually the men are normozoospermic, so, unlike the situation in subfertility, no other useful and widely applicable male seminal parameter exists. In a paper in this issue (Carlini et al., 2017) the authors demonstrate that semen samples from couples experiencing RPL have higher SDF than do samples from either males diagnosed as infertile (Ctrl 1) or fertile males (Ctrl 2). The authors also reported a significant positive correlation between the number of RPL events and an elevated level of SDF. Of interest is that male age was also higher for the group of patient couples with 4 – 6 RPL events, as SDF levels are known to increase with age (Schmid et al., 2007; Alshahrani et al., 2014; Soares et al., 2014).

SDF testing also raises the possibility that changes in male lifestyle and nutrition, or an intervention such as dietary supplementation, may alleviate the damage and therefore avert further pregnancy losses (see, for example, Tremellen et al., 2007; Showell et al., 2014; Dattilo et al., 2016). It is also

important to bear in mind additional potential complexities of dietary effects linked to pesticide exposure that have recently been suggested to affect male parameters (Chiu et al., 2016). Effects related to simple factors such as abstinence, which affect other standard sperm parameters (Bahadur et al., 2016) and DNA (De Jonge et al., 2004) also need to be considered.

A number of systematic reviews over recent years have examined the effect of sperm SDF on IUI/IVF/ICSI outcome (Zini et al., 2011; Osman et al., 2015) but have failed to reach a firm conclusion. The latest systematic review (Simon et al., 2016) found a significant adverse effect of sperm DNA damage on clinical pregnancy rate that varied depending upon the type of assay used. In 2012 a systematic review first confirmed a link between sperm DNA damage and miscarriage (Robinson et al., 2012) spawning a number of subsequent studies, some of which have demonstrated no evidence for the link (Coughlan et al., 2015) and others such as that published in this issue (Carlini et al., 2017) which further support the findings of the 2012 systematic review (Zidi-Jrah et al., 2016; Bareh et al., 2016).

The apparent complexity of studying the effect(s) of DNA fragmentation on fertility is highlighted in Figure 3 of the paper, where it is seen that (i) almost 50% of the fertile group (Ctrl 2) has high SDF, and (ii) the infertile (Ctrl 1) and RPL groups have an equivalent percentage of high SDF (cutoff established by Ctrl 2). In fact, a cursory comparison of the distribution presented in Figure 2 suggests that Ctrl 1 has a broader plateau of elevated SDF compared to the other two groups. These observations mean that SDF cannot be considered a predictive factor for the risk of RPL.

Reproductive medicine does a great disservice to patients when discussing or presenting any of the myriad tests and data as equal to any other based on coalescence of differing evidence. The time has been reached where well-organized data supporting individual tests with prescribed methodology (Barratt and De Jonge, 2010,; Carrell and De Jonge, 2016) is required, along with associated data-assessing efficacy and mechanism of subsequent therapies. In the meantime any clinical offer of SDF testing should make clear to the patient the data supporting that specific test, but the time may indeed be arriving where the potential of SDF testing finally starts to be realized.

Note added: as this editorial was going to press we learned the sad news of the death of Loredana Gandini. Our sincere condolencies to her family and colleagues [http://www.dire.it/06-10-2016/80219-medicina-della-riproduzione-addio-loredana-gandini/]

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