

Adapting sperm RNA as a fertility diagnostic for the male

Infertility is a global public health issue affecting about 13 percent of couples of reproductive age. After one year of unprotected intercourse, couples having difficulties to conceive often seek reproductive care. Known causes of infertility are typically determined prior to prescribing the best treatment for each infertile couple. Male and female factors likely contribute about equally to infertility. Fertility evaluation for men is currently limited to examining subjective semen parameters whereas several diagnostic tests are available to evaluate the female partner. As observed in Figure 1, evaluation of sperm concentration, motility and morphology can resolve obvious cases of male infertility.

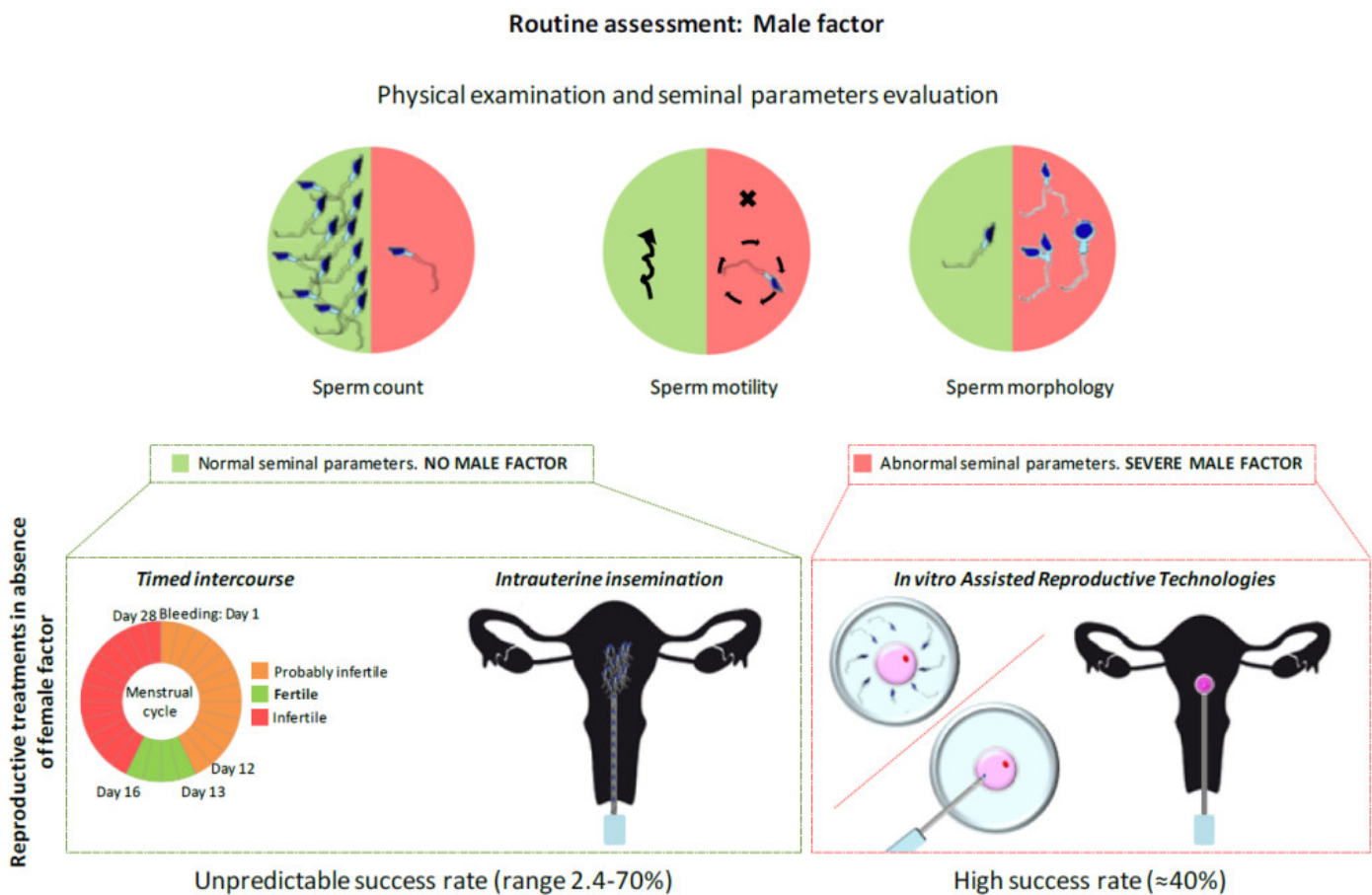


Fig. 1. Standard clinical care of infertile couples based on male fertility status. The evaluation of male infertility factor is based on a physical examination and sperm parameters analysis including sperm concentration, motility and morphology. Reproductive treatments with minimal intervention are recommended in absence of a known female factor and if all seminal parameters are within the range of normal values (green box). These less invasive treatments included timed Intercourse (TIC) that identify the days of the menstrual cycle when the woman could become pregnant and intrauterine insemination (IUI) based on the injection of sperm inside a woman's uterus increasing

the number of sperm that reach and could fertilize the oocyte. In comparison, invasive in vitro assisted reproductive technologies (ART) are recommended if the semen sample has a very low sperm concentration or the sperm has aberrant motility or morphology. In vitro fertilization combines a sperm and an oocyte outside of the body in a laboratory dish with or without the help of intracytoplasmic sperm injection. One or more fertilized eggs that start to develop may then be transferred into the woman's uterus.

For example, this includes a reduced number or the absence of sufficient normal motile sperm to reach and fertilize the oocyte (egg). When a known severe male or female infertility factor is identified the patients are advised to consider assisted reproductive technologies (ART). As shown in Figure 1 (red box), these include *in vitro* fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) with a success rate of around 40%. However a significant proportion of infertile couples (around 20%) do not present any known cause of male or female infertility and are diagnosed as idiopathic. Although ART are also effective in idiopathic infertile couples, less invasive reproductive treatments such as timed intercourse (TIC) and intrauterine insemination (IUI) are the first treatments suggested. This strategy reduces the clinical exposure of the women to intense treatments such as egg collection. However TIC and IUI have unpredictable success rates ranging from 2.4-70% (Fig. 1; green box). This highlights the need for new diagnostic paradigms.

Sperm RNA: New potential strategy in the counselling of idiopathic infertile patients

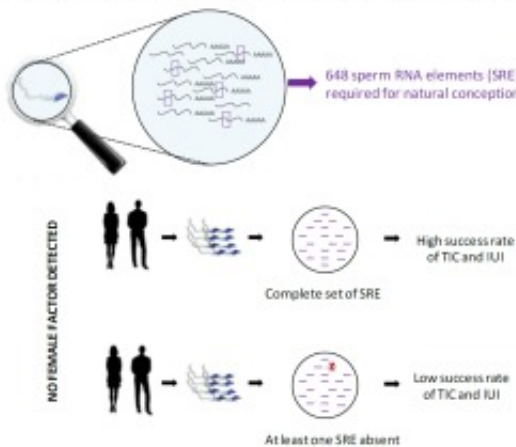


Fig. 2. Sperm RNA as a male fertility diagnostic tool. The study of sperm at the molecular level has resolved the existence of 648 specific regions of different sperm RNAs (Sperm RNA Elements, SRE) required for natural conception. These specific SREs may help counselling patients without any known male or female infertility factor and with good seminal parameters (idiopathic). The presence of the complete set of 648 SREs are associated with a high success rate of the less invasive techniques such as timed intercourse (TIC) or intrauterine insemination (IUI). In contrast, the success rate of TIC and IUI are lower in patient lacking at least one SRE suggesting an early

use of in vitro Assisted Reproductive Technologies (ART).

Though a sperm contains a low quantity of RNA as compared to other cell types, the use of next generation RNA sequencing on sperm of fertile men identified 648 specific regions on different sperm RNAs (Fig. 2) associated with natural conception. These have been termed sperm RNA elements (SRE). About 1/3rd of the idiopathic infertile males included in the study published recently in *Science Translational Medicine* did not have the complete set of SREs. These idiopathic infertile patients lacking at least one SRE had a low success rate to conceive using the less invasive techniques (TIC and IUI) compared to those patients presenting the complete set of SREs. However the presence or absence of the complete set of SRE did not affect the high success rate of ART. On one hand, this suggests that with the complete set of SRE the clinical exposure of the women to intense treatments could be avoided. On the other hand, IVF and ICSI may help to overcome some of the underlying impediments associated with the absence of an SRE. Sperm RNA analysis may be an integral part of standard clinical care to counseling idiopathic infertile patients. With additional studies it may help to identify those couples who may be successful with minimal intervention and those that require more sophisticated technologies. While this may reduce the emotional and financial stress that couples face, the ultimate goal is to safeguard the birth and life of a healthy child.

Publication

[Absence of sperm RNA elements correlates with idiopathic male infertility.](#)

Jodar M, Sendler E, Moskovtsev SI, Librach CL, Goodrich R, Swanson S, Hauser R, Diamond MP, Krawetz SA

Sci Transl Med. 2015 Jul 8