Intra-cytoplasmic sperm injection and infertility

Assisted reproductive technology has revolutionized the treatment of infertility, one of the most common disorders of human health. From the breakthrough of *in vitro* fertilization to the advent of reproductive cloning, each milestone has been accompanied by controversy over the implications for both society and the child-to-be. ICSI is no exception, as this technology now gives virtually all men with severe oligospermia or azoospermia the chance to become a genetic parent[1]. Extremely low sperm counts are thought to be of primarily genetic origin, caused by such factors as microdeletions in the AZFc region on the Y chromosome. With the advent of ICSI, 'sterile' men can now father children who, in turn, inherit their genetic defects[2,3].

The discovery of 25 genes specifically expressed in male germ cells was recently reported in *Nature Genetics*[4]. As most of these genes are on the X chromosome or autosomes, there may be a wider range of sterility-related mutations in women compared with men, although in males, mutations on the X chromosome would skip a generation. These findings suggest that ICSI may precipitate a decline in male fertility in the future, and prompted us to construct a mathematical formulation to forecast the impact of this technology.

Up to 20% of couples worldwide are infertile, including some 2% of male partners who are azoospermic[5]. We used 1:100 as an extreme upper estimate of the overall incidence of genetic defects of spermatogenesis, and used a simple formulation which assumes that an overall proportion (θ) of all these men benefit from ICSI and that any sons they produce will inherit the condition. As these assumptions probably overstate what could happen in practice, they represent a worst-case scenario. We predict a generation-by-generation (i to i+1) increase in the proportion of infertile males, according to:

$$P_{i+1} = \frac{[(1-p_i) \times 0.01 + p_i \times \theta]}{[(1-p_i) + p_i \times \theta]}$$

If half of all affected males underwent ICSI and fathered children, the incidence of severe male infertility would double in seven generations; that is, after approximately 200 years (Fig. 1). If 90% of affected men underwent ICSI, the incidence would almost double to 1.9% in one generation and rise to 6.7% after ten generations. Two factors would prevent the occurrence of total male infertility: (i) socio-economic variables that limit the proportion of men able to benefit from ICSI, and (ii) biomedical progress. Total male infertility could be reached, in theory, if 99% or more of affected males undergo successful ICSI. Although we must remain vigilant about the trans-generational effects of these new reproductive technologies, ICSI will probably not increase overall male infertility in the near future through the widespread propagation of genetic mutations.

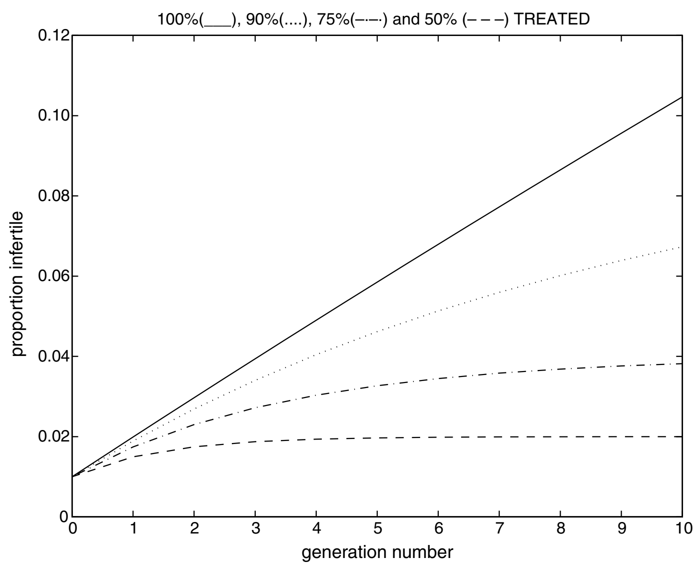

Fig. 1 Predicted incidence of male infertility in successive generations. Results are based on the percentage of men undergoing ICSI treatment because of severe oligospermia or azoospermia.

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