One reproductive option that has long been unrealized is that of choosing the sex of one’s child. This is not for lack of ideas; historically there have been many unproved methods, many fanciful and most now abandoned (Carson, 1988). Conceptions occurring two or three days after ovulation have a slightly increased likelihood of being male, but perhaps only in certain circumstances; at any rate, this observation has little practical value (Gray et al., 1998). Biological based methods have not previously succeeded. Now, Fugger et al. have reported that separation into X- or Y-bearing spermatozoa may be efficacious (Fugger et al., 1998).

Genetic indications for sperm separation are unassailable, and surely few could disagree that selecting a child of a given sex can avoid certain birth defects. Specifically, female infants would not ordinarily be affected with an X-linked recessive disorder; male infants could not inherit an X-linked dominant gene from their affected father, whereas half their sisters would. Family balancing may seem a more contentious indication for sperm separation, but who among us would not in certain circumstances desire an infant of a given sex? Should sperm separation be embraced, or conversely discouraged or restricted?

Considerations

**Does the technology truly alter the sex ratio at birth?**

Mindful of prior claims that have not proved substantiated, a healthy dose of scepticism is proper. Many more patients must be studied, but Fugger et al. (1998) are off to a great start – 13 out of 14 (92.9%) pregnancies of ‘known fetal or birth gender’ had only female concepti or 15 out of 17 (88.2%) ‘of the fetuses’, including three sets of twins. This ratio is consistent with expectations based on the proportion of X-bearing spermatozoa (84.5%) after separation, as shown by using chromosome-specific (Y) probes.

**Is the technique practical?**

There are two problems: (i) sperm separation to enrich for a given sex is not 100% successful, and may never be. This may not be acceptable for all patients; (ii) pregnancy rates seem relatively low, especially in intrauterine insemination (IUI). Couples need to be informed that no guarantees exist, but of course similar counselling applies to any pregnancy: after sperm separation, after assisted reproduction technique (ART) with or without micromanipulation, or after natural conception. A natural cycle carries only a 25% likelihood of pregnancy with mid-cycle coitus, and as well as a 2–3% risk of birth defects. A higher rate of birth defects after sperm separation would be unacceptable.

The pregnancy rate reported by Fugger et al. (1998) is <25%. Our tabulation of their data is shown in Figure 1. It is unclear exactly how many of the 14 pregnancies with known fetal or birth gender came from the intracytoplasmic sperm injection (ICSI)/in-vitro fertilization (IVF) group and how many from IUI, although overall we are told that ‘most’ came from the latter group. The clinical pregnancy rate by IUI was 10.6% (22 clinical pregnancies per 208 cycles), clearly lower.
than the 21.2% (seven per 33 cycles) observed with ICSI/IVF. The abortion rate was 24.1% (seven out of 29); however, the seven are not stratified by group. Depending on the relative number of abortions occurring in the IUI versus ICSI/IVF groups, the IUI ‘take home’ baby rate could thus range from 10% to as low as 7% per cycle (22–7 = 15/208 = 7.2%). If the pregnancy rate were this low in IUI, sperm separation might be attractive only to young highly fertile couples, couples willing to undergo sperm separation in repeated IUI cycles, and couples willing to undertake the expense and exertion of ICSI/IVF.

Is sperm separation safe?

Although a definite concern, we do not believe the problem is insurmountable. The authors acknowledge the theoretical concern of using UV light and the bisbenzimide dye (Hoechst 33342) necessary for fluorescent-based sperm separation, but suggest that the risks may not be so great as the alarmist might imagine (Catt et al., 1997). Bisbenzimide is said not to intercalate with DNA but rather binds to the A–T base pairs in the minor helical groove; thus, binding should be reversible. Bisbenzimide also absorbs UV light at a different wave length spectrum than DNA, presumably mitigating further against a mutagenic effect.

Given extensive animal studies, extant human data, and the theoretical assurances mentioned above, there would seem every reason to proceed clinically. No categorical reassurance can be expected because it will be some time before the sample size confers the requisite power. For example, analysis of 244 neonates would provide a power of only 0.8 (1-α) to detect a three-fold increase (α = 0.05) in anomalies over a background rate of 3%. Almost 1000 cases would be necessary to exclude a two-fold increase over a background rate of 2%. Excluding a specific anomaly would require still a larger sample. Yet, the current situation is no different than when amniocentesis was introduced in 1968 or when IVF was introduced in 1978. These now widely accepted procedures also had their naysayers at the onset. Moreover, our obligation as critical investigators is not to set up roadblocks impeding technology transfer but rather to assure reasonable likelihood of benefit, objective collection of data allowing evaluation of success and complications, and publication of outcomes. Previously published ideas on verifying safety of preimplantation genetic diagnosis apply here as well (Simpson and Liebaers, 1996).

Should sperm separation be allowed?

Is sperm separation to produce an infant of specific gender ethical? Some will doubtless genuflect for proscription. Others will temporize by calling for task forces, conferences, and guidelines that inevitably call for more study and, hence, merely delay the date of an implementation.

The fear seems lost on us. In fact, we argue that it is unethical not to offer sperm separation, assuming efficacy. Since unassailable genetic indications already exist, the technology surely cannot be abandoned. To do so would, de facto, encourage clinical termination after chorionic villus sampling or amniocentesis, the remaining alternatives for many couples. For those merely desiring family balancing, the alternative would be to continue to have children of any sex, increasing societal population burdens.

Just what is potentially contentious about sperm separation for family balancing? One fear is distortion of the sex ratio (106 males: 100 females at birth). Personally we doubt that even a readily available and cheap method would distort the sex ratio, at least not in developed countries. An excess of one gender among 4 year old kindergarten students would surely not go unnoticed, leading to correction toward the suddenly scarce and now more desirable gender. Acknowledging the anxiety of some, however, we favour initially restricting the technology to couples already having one child. This should minimize any short-term distortion of the sex ratio, and as well preclude any distortion based on social advantage seemingly bestowed to the first born child (irrespective of gender).

Conclusion

In conclusion, we finally may have a method of sperm separation that works. It probably will be safe. It is up to society to decide the extent to which it wishes to take advantage of sperm separation technology, but we see no reason to be timid. Both the scientific community and the public have proved wiser and more thoughtful than many have feared. The public and scientific community have previously adapted measured approaches to virtually all new reproductive technologies. There exists barely a scintilla of evidence for untoward application in prenatal genetic diagnosis, gene therapy, preconception planning, and other reproductive technologies. There is no reason to believe the slope will suddenly become slippery.
References


