ORIGINAL ARTICLE

Evolution of gender options in multiple pregnancy management

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ABSTRACT

Objective Fetal reduction (FR) in multiples dramatically improves outcomes. We prioritize FR decisions for health and historically declined to factor gender. As male preferences apparently diminished, our bioethicist encouraged a re-evaluation.

Methods Three hundred ninety-six patients reducing triplets or twins were categorized as 3➔2, 3➔1, and 2➔1, Major (M) anomaly or minor (m) anomaly, same gender (SG), and those for whom gender preference (GP) was possible. Higher order and non chorionic villus sampling were excluded. FR decisions were prioritized by M anomaly, Suspicious, or m anomaly. If neither, we considered GP.

Results Of 319, 214 (67%) had either M/m or SG. Of those, 3➔2 with gender option: 71/79 chose male and female or had no preferences, one chose male/male, and seven chose female/female. We reduced monochorionic twins in 33/35 3➔1 cases. Of 20 with GP choice, 10 chose male and 10 chose female. Of 162 2➔1, 54 had M or m, 50 were SG, but of the 44 M/F twins, 20 chose male and 24 chose female.

Conclusions There has been a cultural shift mostly preferring one of each or having no preference. When reducing to one, >50% prefer a girl. In addition to identifying abnormalities, chorionic villus sampling before FR expands patient autonomy. © 2013 John Wiley & Sons, Ltd.

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INTRODUCTION

In the developed world, the United States in particular, multiple pregnancies continue to be an important contributor to perinatal loss and prematurity even though the incidence of high-order multiples has fallen over the past several years. Chang *et al.* have recently estimated that 0.3% of the 12.5% preterm delivery rate is attributable to assisted reproductive technologies and ovulation induction.[1] By using the $26bn estimate of the Institute of Medicine in 2007 as to the annual financial burden of prematurity, about $624m could be apportioned to such therapies.[2] There has also been an emerging appreciation that the problems of multiples include twin pregnancies not just triplets or more.[3,4]

Fetal reduction (FR) was developed in the 1980s as a method to reduce the burden of fetal loss, prematurity, and its sequelae. Multiple reports have attested to its success.[5–8] Initially, decisions as to which fetus(es) to reduce or continue were largely on the basis of the fetal position and sometimes ultrasound concerns but were independent of any cytogenetic or molecular diagnosis. This is still true for most FR providers. Many groups have reported on the variable efficacy and additional limitations of screening tests in multiples as there is commonly confusion as to which fetus an abnormal screening test is attributable.[9–13] We, and a small number of other groups who developed and have extensive experience in chorionic villus sampling (CVS) in both singletons and multiples, began to routinely offer CVS prior to reduction in the late 1990s, which we believe offers a significant opportunity to improve the likelihood of healthy families for these patients.[14–16]

Because of the advent of prenatal diagnosis techniques with the development of amniocentesis and ultrasound 40 years ago and CVS 30 years ago, their use (abuse) merely for the identification of gender with termination of normal females was a consistent although minor component of cases in the United States and many Western European countries. Although essentially never rigorously documented or justified in either medical publications or national statistics, the United States may be broadly characterized as being relatively neutral with respect to gender preference.[17–24] Prenatal diagnosis for gender selection has been much more common in certain other countries such as India and China, although a recent

paper concludes that a gender imbalance still exists in Chinese, Asian Indians, and Koreans in the United States.[24–27]

In the United States, physician reactions to requests for gender selection over the past decades have commonly been very negative and reflect the inherent dilemma between patient autonomy and a physician's right not to participate in activities that violate their own ethical code. Our general philosophy (MIE) since the 1980's was that 'we believe in the diagnosis of genetic disease, but that being female is not a disease'. Ironically, the vast majority of 'appropriate' gender related cases were for X-linked conditions, for which being female was usually the desired outcome. When we did receive requests for prenatal diagnosis merely for gender or to terminate a normal female fetus because of its gender, we refused to participate. We have no doubt that some of the indications for prenatal diagnosis that patients declared (e.g. previous Down Syndrome in a 25 year old) were bogus, and after we declined to terminate a normal female fetus, some patients did find other providers who would accommodate them. There are no rigorous publications on the incidence of patients lying to physicians under these circumstances, so by definition, all such data and conclusions are anecdotal. However, our group has decades of experience in prenatal genetic counseling and diagnosis and arguably is in a better position than most to comment about patients' concerns and preferences.

Given that the majority of our patients have been over 35 years old, we began to add CVS with fluorescence *in situ* hybridization analysis prior to FR in continually increasing percentages. Aneuploidy, including sex chromosome abnormalities, was added as a primary criterion in decision making. For many years, we still declined to incorporate genetically normal gender preferences, but informally, we began to notice that there was a shift in patient's stated preferences to be much more even and to come from patients of all ethnic backgrounds. After extensive discussion over a period of several months in 2003 and 2004 with our long time bioethical consultant (John C. Fletcher, PhD), we decided to consider such requests in cases in which there was no medical advantage relevant in the choice. Here, we report from our experience in our last 400 cases from 2007 to 2010 of triplets reduced to twins or singletons, and twins reduced to singletons. As there are very few groups worldwide with comparable experience and even fewer who routinely perform CVS prior to FR, it is not possible to have reasonable comparison groups for our program.

MATERIALS AND METHODS

Over the past three decades, we have refined the process of decision making in FR cases. For approximately 85% of patients, we perform CVS and fluorescence *in situ* hybridization for chromosomes 13, 18, 21, X, and Y for which we obtain results the next day. Then, by using all available information, we proceed with the FR on the second day as we believe the benefits of next day procedures to reduce errors in identification and eliminating a second trip (often great distances) outweigh the small risk of clinically relevant findings on the final karyotype.

We prioritize FR decisions by (1) Major (M) anomaly including aneuploidy or major structural anomaly such as cardiac or CNS, increased NT >3 mm; (2) Suspicious or minor (m) findings such as somewhat increased nuchal translucency (>2 mm), smaller fetal size (such as more than one half week, smaller gestational sac size, or placental concern); and (3) If none of the above apply, then and only then, we will consider gender preference. Patients are told that they will have a nongender disclosing 'poker faced' discussion with them when we obtain the results. They will then choose which of the four categories concerning gender they prefer. The groups are as follows:

(1) Those patients who want to know 'everything',
(2) Those who want to know 'nothing',
(3) Those who have no preference but want to know what they have kept (but not the reduced), and
(4) Those who, all things considered, do have a preference (but do not want to know the reduced fetus or fetuses' genders).

We retrospectively reviewed our patients' choices in our last 400 patients who started with triplets or twins and who had CVS usually on all fetuses followed by FR. Patients were categorized as those reducing from: 3➔2, 3➔1, and 2➔1. We then categorized those for whom (1) no gender choice was considered because they had either M or m findings, or all fetuses were the same gender, and (2) those for whom a gender choice was possible by the earlier criteria. Statistical analyses were performed by X^2 as appropriate. This study was approved as 'exempt' by the institutional review board of the Albert Einstein College of Medicine.

RESULTS

Overall, 253 of 396 patients (64%) did not have any gender choice by our program's criteria. These patients had either Major anomalies (M)/minor ultrasound findings (m), did not have genetic testing, or all fetuses were of the same gender (Table 1). Of those having CVS prior to reduction, 215/358 (60%) did not have any gender options.

Seventy-nine patients reducing from triplets to twins did have a gender option by our criteria; 71 of the 79 reduced to one male and one female (Table 2). One third of these patients had a

Table 1 **Distribution of fetal reduction cases without gender option**

	n	Anomaly*n* (%)	Mono/di pair*n* (%)	Fetal sex unknown* *n* (%)	All male or all female fetuses*n* (%)
3➔2	154	18 (12%)	2 (1%)	20 (13%)	35 (23%)
3➔1	80	5 (6%)	35 (44%)	4 (5%)	16 (20%)
2➔1	162	54 (33%)	NA	14 (9%)	50 (31%)

NA, not applicable
*did not have prior genetic testing.

Table 2 Fetal gender options and choices

	Gender option *n* (%)	Chose all male *n* (%)	Chose all female *n* (%)	Chose male/female twins *n* (%)	*p*
3➔2	79 (51%)	1 (1%)	7 (9%)	71 (90%)	<0.001
3➔1	20 (25%)	10 (50%)	10 (50%)	NA	NS
2➔1	44 (27%)	20 (45%)	24 (55%)	NA	NS

NA, not applicable; NS, not significant

strong preference for one of each, one third had a mild preference, and one third declared no preference. Their preferences were statements – as opposed to any specific scoring. Of the remaining eight patients, one desired two boys, and seven wanted two girls ($p < 0.001$). Overall, an anomaly was the deciding factor for which fetus to reduce in 12% of triplets reducing to twins, 6% of triplets reducing to a singleton, and 33% of twins reducing to a singleton. A monochorionic twin pair was the primary consideration in 44% of triplet to singleton cases. All fetuses were the same gender in 101/396 (25.5%) of cases. Only 2% of patients wanted to know the gender of reduced fetuses.

Nearly half of triplets reducing to a singleton included Monozygotic twins for whom we reduced Monozygotic in 33/35 cases. Of 20 triplets reduced to singletons for whom there was a gender choice possible by our criteria, 10 chose male and 10 chose female. Of 162 twins to singleton cases, 54 had major or minor abnormalities, 12 did not have a gender diagnosis obtained, and 50 were both the same gender. For those 44 with a male/female twin pair, 20 preferred a male and 24 preferred a female (Table 2).

To investigate whether some of the gender choices were different in couples who did not already have children (e.g. was there a preference for a boy for the first child),we repeated the analysis on primiparous pregnancies. We found no significant differences in the distributions (Table 3).

COMMENT

Since the beginning of our experiences with FR, we have been cognizant of the ethical dimension including how patients make decisions, how they 'frame' their decisions, and how they communicate these decisions with their families and friends.[28–35] We have worked together with both ethicists and sociologists and published multiple studies on these issues.[28–35] For our patients, at least, we have perceived a definite shift in couples' approaches to gender selection in FR cases over the past 25 years. Because we would not entertain gender preferences for many years, we did not keep rigorous data on that issue, so by that definition our experience is anecdotal. Furthermore, there have been no such rigorous studies on gender for multiple pregnancy and reduction patients. Thus, our data might be considered anecdotal in that they are based on case notes and discussions for women who are somewhat older, somewhat more educated, probably somewhat wealthier (or at least have good insurance), almost all of whom have gone through infertility therapies of one sort or another and find themselves facing an extraordinary set of decisions in order to manage their pregnancies – rather than being on the basis of a random sample of women who are intending to have children.

A counter argument (which we support) can be made; however, for these data having a great deal of rigorous, scientific credibility. One of our group (MIE) has been the constant presence interviewing these women as part of a rigorous informed consent process. Each patient must discuss exactly what is being performed and what the potential consequences are. Part of this, of course, is to respect the informed consent process and not let patients slide through the procedure with their eyes and minds closed. From a data credibility point of view, however, this procedure reinforces the salience of the decisions that are being faced *in situ* as opposed to the conditions that are the rules in most conventional surveys. Our analytical approach incorporates qualitative methodology, which is standard and universally accepted in the sociology literature.[36] We would not presume to generalize directly from this sample of women to the society at large, but it does seem reasonable to suggest that the information that comes from such a sample of informed women going through a highly emotionally charged period in their lives regarding gender preferences should be given the status associated with key informants in qualitative investigations.

From this perspective, we perceive there to be a cultural shift in such patients over the years but certainly agree that generalizations, beyond our patients and multiples considering reductions, need to be interpreted cautiously.

Table 3 Fetal gender options and choices in primiparous pregnancies

	Gender option*n* (%)	Chose all male*n* (%)	Chose all female*n* (%)	Chose male/female twins *n* (%)	*p*
3➔2	50 (69)	1 (2%)	5 (10%)	44(88%)	<001
3➔1	7 (10)	3 (43%)	4 (57%)	NA	NS
2➔1	15 (21)	7 (47%)	8 (53%)	NA	NS

NA, not applicable; NS, not significant

Although we did not publish our experience on gender preferences and requests from 20 years ago, in the early 90's, the majority of such requests appeared to us to come from couples of ethnic groups for which there was a significant male preference. More recently, expressed preference appears to come from patients of all ethnic backgrounds and, if anything as shown by our data, is slightly more in favor of a girl than a boy.

Our patient population comes from all over the United States and a small percentage from abroad. The ethnic background has remained over the past 25 years at approximately 90% Caucasian, 5% Asian, 2% African American, 1% Arabic, and 2% Asian Indian. We have seen some equalization of preference choices in multiples for those patients of Asian, Indian, and Arabic backgrounds from previous male preference, but the numbers are too small to have statistical meaning.

What was more common 20 years ago were requests from patients with singleton pregnancies of those ethnic groups for males (unpublished). These have, to a large degree, disappeared from our program – either because it became known we would not perform prenatal diagnosis for gender, *per se*; these patients found other providers who would do so, or as we believe, there has been a change in the culture in the United States that has equalized the perception of women even from 'traditional' cultures such that fewer couples have such wishes. We are in no position to make any truly generalizable statement about culture across all groups in the United States, but we are in a unique position to put forth these observations as a predicate to future, broader studies.

Our data show that for those couples for whom there is the possibility of choosing gender in FR cases (by the criteria we describe earlier), the concept is acceptable to a majority but certainly not to all patients. Reactions varied across the spectrum from clear preference for a specific result, to mild statement of interest, to those who wanted no input whatsoever, some of whom described unhappiness with a feeling they had any choice in the matter. We counsel our patients that we categorize gender preference to be an 'afterthought' to be considered only if nothing else matters. We have explored with them the strength and conviction of the couples on this issue (real time) without changing the focus of the medical care on reducing pregnancy risk, which always remains our primary goal.[29–35] Overwhelmingly, however, patients reducing to twins, who did express preferences, wanted one of each, followed by two girls, and least preferred were two boys. A small percentage of patients voiced a specific desire for family gender balancing. Overall, we did not find any significant differences in preferences in primiparous versus multiparous pregnancies (Table 3).

Fetal reduction was developed in the 1980's to ameliorate poor outcomes seen in higher order multiples that are a consequence of infertility therapies.[5–8,34,35] There is an extensive literature on the issues surrounding multiples and FR that will not be repeated here other than to emphasize that multiples now constitute 3% of all births in the United States and a disproportionate share of prematurity and its sequelae.[1–4] Furthermore, FR has followed the same developmental pathway as several other originally radical new technologies, such as fetal surgery, in that the first cases performed were performed only in 'life or death' situations. As understanding of the risks and benefits emerge, indications eventually liberalize to include 'quality of life'.[37,38] Data in the last decade have confirmed that FR significantly improves the outcome of triplet pregnancies and have shown that even for women starting with twins, that if one defines success as a healthy mother and family, reduction improves outcomes.[35] Although the improvements from twins are not as substantial as starting with quintuplets, for example, they are real – both for pregnancy loss and neonatal morbidity.

The possibility of gender selection with FR adds another dimension to an already complex and, to some, still very controversial process. From an ethical perspective, we (Evans and Fletcher) developed our initial ideas and wrote much of the early literature on FR in the late 1980's.[5,6,28–35] Analogous to our work on fetal therapy, we concluded that we should begin with those cases and procedures for which there was 'nothing to lose' and as such would likely have the most medical and lay support.[37,38] We concluded then that, except in extremis, we should not reduce down to a singleton; likewise, in the absence of X-linked genetic disease issues, including gender as a factor, was not appropriate given the then heavily skewed preference for males from those couples making such inquiries. As patient preference has evolved with time to a relatively equal desire for females and males, however, so has our practice. A very small percentage of our patients (~2%) had prior preimplantation genetic diagnosis for gender preference and appear to be equal in gender preference – but the numbers are too small for statistical analysis. Some critics will argue that any acknowledgement or agreement to honor wishes of parents about gender preference is inappropriate. We certainly respect such opinions, and in fact many of our parents have no preference and do not even want to know if there were a choice possible. We came to the belief, however, that because of balance in preferences, the argument of inherent sexism diminished, and as a result, that parents should be given such input when reasonable.

We have long believed that, in part, ethical conclusions evolve with technology.[5,6,28–35] We and many others have written on this subject that has filled volumes.[5,6,28–35] The ethical principles of autonomy and proportionality, that is patients controlling their own destiny and achieving the most benefit for the least harm, are paramount. Given that gender is never used to decide 'if' there is going to be a reduction procedure, but only which among apparently normal fetuses is to be kept, beneficence is maximized in that resulting children are very much wanted.

What has changed in this field over the last 20 years are that (1) rapid, reliable diagnosis of common aneuploidies became common practice for us, and (2) we perceived a significant change in the sociologic dynamics of couples'

thinking to include desire to have a choice with a concomitant evening out of gender preference. A limitation of our data is that our patient base reflects a bias as to who actually seeks our services. Our experiences reported here reflect changes in our population and may or may not be generalizable.Our data and perceptions from discussions with our couples, however, are consistent with the concept that gender selection, when chosen by couples, reflects commonly a desire for family balancing with an equalization of the perception of worth of females in our society. We see this as a positive development.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Fetal reduction significantly improves outcomes in multiples; fetal gender in the decision has generally been unavailable or deliberately ignored because of historical biases against females.

WHAT DOES THIS STUDY ADD?

- We routinely obtain genetic studies before reduction. We report here an apparent major shift in culture such that now females are as equally desired as males. As such we feel justified in allowing gender to be a secondary determinant in FR cases.

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