Abstract

The prevalence of high-order multiple (HOM) pregnancies has increased because of ovulation induction, assisted reproductive technologies, and spontaneous conceptions in older mothers. Pregnancies with 3 or more fetuses carry heightened morbidity and mortality risks for mothers and children. Although many families cope well, psychosocial complications include stress, marital and financial strain, social stigma, depression, grief, and neglect of multiples and their siblings. Adequate support reduces adverse consequences. Multiple births strain societal resources. With fertility treatment, the desires of patients, business pressures of clinics, and financial, legal, and religious considerations influence HOM conception rates. Maternal autonomy in fertility treatments must be balanced against obligations to prospective children and society. Selective termination of abnormal fetuses and multifetal pregnancy reduction are ethically justifiable, but may contradict parents’ or clinicians’ values. Decisions for moribund multiples are difficult. Media coverage is often inaccurate or intrusive, but benefits some families. Skilled care, accurate information, and practical resources optimize outcomes.

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Ethical Issues of High-order Multiple Births

By Elizabeth A. Pector, MD

The incidence of high-order multiple (HOM) pregnancies with triplets or more has increased 4- to 8-fold in developed nations since the late 1970s. In 2002, HOM births accounted for 184 per 100,000 deliveries in the United States. About 40% of such births result from ovulation induction (OI) with fertility drugs. Another 40% involve assisted reproductive technologies (ART), such as in vitro fertilization (IVF) with embryo transfer, intracytoplasmic sperm injection, gamete (sperm and ova) transfer to the fallopian tube, or zygote transfer to the fallopian tube. The remaining 20% of HOMs occur spontaneously. One fifth to one third of the increase in multiples is attributed to spontaneous conceptions in older mothers (Ref.6, p 11; Ref.7). This article reviews unique medical, familial, societal, and ethical aspects of HOM births and fertility treatments. Resources are provided for professionals and affected families.

Medical Consequences of HOM Pregnancies

Maternal morbidity and mortality are greater in multifetal pregnancy than in singleton pregnancy. Women expecting HOMs are at an increased risk of preeclampsia, eclampsia, pregnancy-induced hypertension, anemia, gestational diabetes, preterm labor and delivery, pulmonary edema from beta agonists used to halt preterm labor, incompetent cervix, cesarean section, placental abruption, and postpartum hemorrhage. Mothers may be hospitalized on bed rest for prolonged periods. Therefore, diagnosis of a multiple conception must be given to parents sensitively, as they may react with shock or anxiety in addition to joy.

Approximately one fifth of families with triplets and one half of those with quadruplets have at least 1 disabled child (Ref. 6, p 256) due to anomalies and prematurity. The chance of at least 1 fetus in a multifetal pregnancy having an anomaly or chromosomal defect is higher simply because more fetuses are present. Furthermore, an increase in anomalies in children conceived via IVF or intracytoplasmic sperm injection has been suggested, and monozygotic (MZ, identical) multiples have a greater than usual rate of malformations (Refs. 4, 6, p 150–4; Ref. 12). Of all triplets, 6% are MZ and the others are trizygotic (3-egg fraternal) or an MZ pair with a DZ (dizygotic) sibling (Ref. 6, p 15). Most multiples conceived with assistance are polyzygotic, but MZ multiples occur more often after ART than expected (Refs. 4, 6, p 15; Ref. 13). Monochorionic (MC, shared placenta) multiples in a HOM pregnancy are at risk for twin-to-twin transfusion syndrome and monoamniotic or conjoined twinning. For these and other reasons, zygozy must be determined as early as possible.

Even more significantly, perinatal morbidity is greater for HOMs, chiefly because of premature delivery. More than 90% of HOMs are born
prematurely (Ref 6, p 256), with mean gestational ages for triplets of 32.2 weeks, quadruplets, 29.9 weeks, and quintuplets +, 28.5 weeks.2 Premature HOMs may develop respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, mental retardation, developmental delay, and cerebral palsy.1,4,7,8 Moreover, MC surviving multiples have an increased risk of cerebral palsy and other morbidity after intrauterine death of their MC comultiple.4,8 In all, cerebral palsy prevalence is 3% to 8% for triplets1,8 and 11% for quadruplets.1 Blickstein and Keith1 cite a report by Francois et al of 30% neonatal morbidity in 30 quintuplet pregnancies delivered after 24 weeks. For unclear reasons, poor outcomes for HOMs may be more common after fertility treatment than in spontaneous multiples.1,8

Finally, perinatal mortality is greater in HOMs. UK data from 1999 revealed a combined stillbirth and first-month neonatal mortality rate of 40 per 1000 for twins, but 65 per 1000 for triplets. In addition, US infant mortality in 2002 was 63.2 per 1000 for triplets and 95.5 per 1000 for quadruplets.14

Family Consequences of HOMs

Caregivers must put risks in perspective for patients. Most babies and families thrive.9,11 However, raising HOMs is exhausting and stressful, and parents’ coping abilities vary.15,16 Mothers of multiples leave the workforce more often than mothers of singletons.17 A family’s financial status may decline, with reduced income and increased costs of medical care and home help.18 Socioeconomic status influences outcomes. For instance, older mothers’ HOM infants fare better than those born to younger mothers, but perinatal mortality and very low birth weight increase when older HOM mothers are poor.1 Moreover, despite equal perinatal loss rates, postneonatal infant mortality is higher for black than for white US triplets.19 Media coverage does not improve financial status, except for families with 5 or more babies who reluctantly trade privacy for corporate sponsorship.20 The positive attitude and coping abilities featured in reports about such high-multiple families may create a sense of failure in parents struggling to manage fewer multiples with much less help.16,21 At worst, publicity may generate negative attitudes toward HOM families,16,22 evident in stigmatizing comments heard by parents, such as “How dare you mess around with God’s will?”16 or “There are reasons for birth control” (Ref. 23, p 364).

Help with feeding, bathing, and diapering infants is mandatory,10,15 because caring for 3 babies requires 197 hours instead of the 168 hours actually present in a week.15 Mothers who want to breastfeed deserve respect, encouragement, and informed guidance (Ref. 23, p 241–61; Ref. 24). Support often comes too little, too late, as a family’s needs outlive the typical 1 year of aid from public sources, friends, or relatives5,9,18,20 However, parents may not ask for help, feeling their request implies that they cannot cope.15

Although a secure marriage promotes mental health for a mother of multiples, relationships may be compromised by struggles with subfertility and ART.18 Some marriages are strengthened,16 but divorce may be more frequent among parents of multiples, especially if they are not well-supported in the first year.15 Parents of multiples often become isolated from peers,20 and they may feel incapable of meeting the competing needs of several often premature or disabled children (Refs. 18, 23, p 297–323; Ref. 26). Parents of twins perceive their stress as greater if their twins were conceived with IVF rather than spontaneously.16,27 A recent study revealed severe stress in 22% of first-time mothers of IVF twins and triplets, but no decline in mental health.17 In contrast, other studies show more frequent depression and anxiety, perinatally and later, in mothers of multiples than mothers of singletons.15,16,26

Some multiple-birth fathers express anxiety, sadness, frustration, demoralization, and bitterness about changes in their marriages and their wives’ mental health.16,26 Optimally, fathers should adjust professional and leisure activities, and help at home.18 They may at first be more involved with multiples than with singletons,18 but their involvement may wane.18,26

The psychosocial and educational experiences of children growing up among higher multiples are not well-studied (Refs. 5, 23, p 425–45, 495–531; Ref. 28). Multiples’ interactions with peers may be affected by having a built-in social group (Refs. 5, 23, p 425–47, 495–531; Ref. 28). MZ multiples may be very close, whereas DZ comultiples may feel their MZ wombmates exclude them (Ref. 23, p 509–31; Ref. 28). Single siblings born before multiples may feel neglected (Refs. 5, 10, 20, 23, p 322–8). Multiples have a greater risk of learning difficulties.11,26 If 1 multiple is disabled, healthy comultiples may be close allies, but they also may envy the attention the disabled child receives and they may feel guilty for escaping disability themselves.20 HOM babies receive less stimulation from holding, eye contact, and speech than singletons.9 Depressed parents have lower-quality interactions with their children,15,18,26 and child abuse occurs more often to multiples and their siblings15,25,26 especially in the presence of marital, family, or financial disturbance, parental depression, prematurity, neonatal complications, or isolation.26 Finally, the well-being of multiple-birth children has not been studied in nontraditional families with single parents, postmenopausal mothers, or same-sex
couples, although ART-conceived singletons in such families exhibit good adjustment.29,30

Families who experience the death and/or disability of multiples grieve the loss of their expected outcome while caring for any survivors, and parents with these burdens have higher rates of depression.15,16,31 Parents may experience prolonged, complicated grief when they lose all of their multiple-birth children, especially after fertility treatment.31 Moreover, couples who lose 1 multiple grieve as deeply as parents who lose a singleton,11,31 but their grief may be delayed while they attend to their remaining children.31 Some bereaved parents have difficulty attaching to surviving babies.31 Parental grief may be underestimated by acquaintances who may call 2 remaining children twins instead of surviving quadruplets.31 Finally, reliable help and respite care can ease stress for parents with chronically disabled children.11

**Economic and Societal Consequences of HOMs**

The financial burden of caring for a woman expecting multiples, and later for her neonates, usually shifts to insurers or the government.5,15 Strong7 quotes the 1994 year in the United States.4 Improved IVF technology would save $280 million each label assisted conceptions would save $80 million and Blickstein and Keith estimate that eliminating uncontrolled care cost nearly $295,000, whereas a 26-week infant's treatment totaled more than $166,000.9 True costs are even higher, because these estimates do not include income lost by mothers at home on bed rest before birth or caring for children afterward, physician fees, emergency transport for pregnant women or neonates, outpatient care, in-home assistance, or therapies for children with special needs.12 Blickstein and Keith estimate that eliminating uncontrolled assisted conceptions would save $80 million and improved IVF technology would save $280 million each year in the United States.4

The need for special care for extremely premature multiples can overwhelm the capacity of neonatal intensive care units,4 sometimes requiring separation of a set of multiples among 3 or more hospitals—a logistical nightmare for families (Refs. 8, 23, p 202–4). Conversely, a hospital that is reserving beds for an impending HOM delivery may not be able to accept an ill singleton.20 Some hospitals expand their neonatal intensive care units because of a regional increase in premature multiples.7

Finally, families of multiples depend increasingly on extended family and communities, because fewer companies offer discounts or free merchandise.5 A UK study found that both statutory and private help were inadequate and delayed.20 The responsibility for education, therapy, health care, and assisted living for disabled adult multiples will strain future community resources.5 Denton and Bryan believe the drain of ART-conceived multiples on publicly funded health, educational, and social services merits public policy debate.20

**Ethical Dilemmas Involving Fertility Treatments and HOMs**

Table 1 summarizes biomedical ethical principles considered by specialists who perform fertility treatments and prenatal interventions. Individual moral perspectives may conflict with these principles, leading to disagreements between patients and professionals and within couples and caregiving teams. These differences may emerge as criticism, blame, or anger and impair communication at critical moments. Professionals must provide full and accurate information to facilitate truly informed consent, and must respect decisions that vary from their recommendations. The following discussions, combined with the foregoing background information,
highlight the difficulties of balancing and distributing risks and benefits among prospective or expectant parents, children not yet conceived, fetuses, ill neonates, HOM families, and society.

**Fertility Treatments**

One ethical dilemma involves the risk of multiples from fertility treatments such as ART and OI. Couples and society may view childbearing as a duty or right, but insurers may view fertility treatment as experimental or unnecessary to preserve health. OI is much less expensive than IVF and is morally more acceptable to some couples. However, practitioners cannot easily control the number of fetuses conceived, and OI clients who would not consider multifetal pregnancy reduction (MFPR) ought to monitor ovulation with ultrasonography, abandoning cycles with great risk for HOMs. The aim of fertility treatment is birth of a single healthy child and European countries report acceptable IVF pregnancy rates in some patients using single-embryo transfers. However, more than one third of ART-conceived live births in the United States in 2001 were multiples, with nearly 4% HOMs. Multiples are an unintended outcome, but reproductive clinics may employ approaches that increase multiples in their efforts to achieve competitive pregnancy rates. Regrettably, success statistics do not distinguish between single and multifetal pregnancies. Flexible voluntary guidelines for the number of embryos transferred are preferable to governmental regulation of IVF. American Society of Reproductive Medicine guidelines may be lowering US HOM conceptions, but they still allow transfer of up to 5 embryos, whereas Europeans transfer 3 or fewer.

Ethically, physicians must balance the autonomy of the subfertile woman against their obligations toward potential children, the family, and society. Parents do not usually plan multiples, but some, including a reported 67% in the 1995 study of Gleicher et al, and 20% surveyed more recently would welcome twins from fertility treatment. Partners’ desires may differ, but Gleicher et al reported that only half of subfertile couples objected to possible triplets. Emotional duress, treatment costs, and insurance constraints often pressure couples to achieve pregnancy promptly, even with multiples. Parents’ informed consent is impaired by emotions, slanted media portrayals of successful multiple births, unrealistic expectations, and inadequate information about psychosocial consequences of multiples.

The best interests of potential child(ren) are not consistently taken into account in fertility treatments. For instance, nontraditional families, such as same-sex couples, single women, or postmenopausal women may receive ART, despite arguably unwarranted controversy about the children’s well-being. In addition, religious principles or national legislation may increase HOM risk by allowing only OI, prohibiting IVF, requiring transfer of all embryos fertilized in an IVF cycle, or prohibiting abortion. Moreover, although justice calls for equal treatment access and outcomes for rich and poor, ART is not equitably distributed in any country, and discrepant US outcomes related to income and race were noted above.

In looking at the big picture, several writers believe fertility specialists should not intentionally create multiples to fulfill a client’s request for them, even if clients believe they can raise them, because of child and family risks.

**Multifetal Reduction and Selective Termination**

A second ethical controversy concerns 2 procedures that may avert complete pregnancy termination and improve outcomes for HOM pregnancies. The first of these, selective termination (ST), is usually performed in the second trimester and is considered when one or more fetuses in a multiple pregnancy have an anomaly that is unacceptable to parents. It enables the healthy birth of unaffected comultiples. The second procedure, MFPR, is usually performed in the first trimester to terminate one or more fetuses in a high-order gestation so that a smaller number of remaining fetuses will more likely reach a viable gestational age and escape disability. Evans et al believe these procedures enable pregnancy to continue with the least harm and most benefits to all involved. Individual patients assess risks differently. Patients who oppose abortion for all reasons may find these procedures unacceptable.

An ethical concern in ST is the risk for normal comultiples. At skilled centers, total pregnancy loss rates after ST are similar to spontaneous pregnancy loss rates, and deliveries occur at a better gestational age than would be expected with the original number of fetuses. Thus, withholding ST out of concern for harming healthy fetuses is not justifiable, because ST may even improve their chance of survival. Evans et al consider ST to meet the “most good-least harm” ethical principle, but they recommend it only before viability. Berkowitz ordinarily does not offer ST for lethal anomalies, preferring to allow spontaneous death and avoid an invasive procedure with even small risks for a normal fetus, unless a condition such as anencephaly or conjoined twins jeopardizes healthy comultiples. ST for severe twin-to-twin transfusion syndrome may be contemplated when death of 1 twin is
imminent, but must be timed carefully to avoid death or morbidity to the remaining fetus. In making their decision for or against ST, parents consider medical aspects of the fetus’s condition, plus its short- and long-term impact on healthy fetuses and the family.  

Many authors have discussed ethical and moral issues of MFPR. Prevention of multiple gestation is preferable to an emotionally and ethically challenging reduction. MFPR creates a conflict between the duty to preserve a wanted pregnancy so that it does not pose undue physical or mental harm, and the duty not to destroy human life (even previable) without justifiable reasons. Some parents, including some who otherwise oppose abortion, justify MFPR for the life and well-being of the remaining fetuses, whereas others consider it unethical to terminate an apparently healthy fetus for any reason. Berkowitz draws an analogy to a crowded lifeboat after a sea disaster. Too many passengers will cause the vessel to sink, with all lives lost, yet those who are not brought on board will die. Seen this way, the decision for MFPR may be easier for a woman carrying 8 or more fetuses, but difficult with fewer, and parents sometimes disagree.

Outcomes after reduction depend on the starting number of fetuses. Complete pregnancy losses are more frequent, and gestational age at delivery is lower, when there are 4 or more starting fetuses rather than 3. Regardless of initial fetal number, Luke et al found preterm birth and growth restriction to be more frequent in pregnancies reduced to twins than in pregnancies starting as twins. Still, there may be advantages in reducing triplets to twins. For instance, 11% to 20% of unreduced triplet pregnancies miscarry before 24 weeks, but only 4.5% to 7.6% of pregnancies miscarry after triplets are reduced to twins. Reduction to a singleton for nonmedical reasons, especially from twins, is controversial. Berkowitz does not find it justifiable. Evans et al finds it reasonable for women who conceive after their mid-forties, and Chervenak and McCullough feel maternal autonomy justifies reduction to a singleton if parents only want 1 child.

Although most patients ultimately feel they made the right decision, MFPR is distressing, with average grief for 1 month. Positive feelings 2 weeks after the procedure and 6 weeks after delivery may turn to negative feelings 6 months after delivery. Guilt, grief, or depression persists in one fourth to one third of parents, generally but not invariably resolving by 2 years after the procedure. Patients who see the fetuses more on ultrasound or who are more religious or younger may be more at risk for prolonged psychological distress. A few parents wish to know about evidence of reduced fetuses at delivery. Short-term follow-up indicates children born after MFPR are thriving. Although parents wonder, it is still undetermined whether parents should tell remaining children about the MFPR. If told, the living children could conceivably feel they survived arbitrarily at a sibling’s expense or they could view their parents as murderers. Couples need better information about possible multiples before ART, and thorough counseling before reduction and as long as desired afterward, because many couples keep ART or MFPR secret and cannot confide in anyone else. Similarly, physicians and nurses must strictly protect parents’ secrets about MFPR when remaining children are born and can ask how parents refer to them as a set (eg, by their names or as “the babies,” not “the twins”).

Balancing Children’s and Parents’ Interests in Perinatal Decisions

A third ethically sensitive area involves perinatal interventions that benefit some babies but expose others or the mother to risks, such as preterm delivery of all babies because one is distressed, and delayed delivery of remaining fetuses after one is born prematurely. Also difficult are decisions for severely ill multiples. In a retrospective survey, most bereaved parents of multiples described independent consideration of each child’s prognosis, apart from the status of comultiples. They held a range of perspectives on care, from wanting life support withheld or withdrawn when doctors predicted a vegetative existence to requesting everything possible to sustain life. Some caregivers criticized parents’ preferences. Important to parents were collaborating with doctors on decisions, seeing children alive before their death, being informed about death sensitively, reviewing cause of death with physicians, and having private time, photos, and mementos with multiples together.

Clinicians’ Ethical Conflicts and Practical Obligations

Fourthly, a patient’s or colleague’s decisions may contradict a professional’s personal values. Philosophers, physicians, and nurses repeatedly ask, “How can a couple do this to their baby?” when considering “damaged” multiples born after fertility treatment. Some argue that death is more compassionate than a burdensome life without pleasure, whereas others believe even a handicapped life has value to a person who would otherwise not have been born. Physicians or parents may nonetheless be seen as morally responsible for endangering children by creating or continuing a HOM gestation. Doctors and nurses may justifiably refrain
from interventions such as MFPR that violate their own principles, but they have a duty to inform patients nonjudgmentally of options, to respect their autonomy in self-determination, and to refer them to qualified practitioners for requested services.\textsuperscript{3,33} Physicians, nurses, and midwives work with HOM families long-term, and they appreciate venues to discuss ethical and moral dilemmas.\textsuperscript{14,44} Regardless of their personal values, caregivers can offer unbiased information before, during, and after a HOM pregnancy regarding medical and psychosocial risks,\textsuperscript{9,13,16,20,22,40} available interventions,\textsuperscript{3,4} financial and practical preparation,\textsuperscript{10,11,22} mental health needs (Refs. 18, 23, p 297–313; Ref. 26), and peer support.\textsuperscript{10,11,22,31} Parents greatly appreciate honest discussions.\textsuperscript{14,21} Resources in Table 2 offer realistic information. Moreover, a coordinated team approach is essential for prenatal, neonatal, and infant care.\textsuperscript{10,11,22,31} Parents value convenient outpatient scheduling, which may include home visits by physicians, nurses, therapists, lactation consultants, and even hospice workers (Ref. 23, p 70–2, 198–202; Ref. 31).

### Journalistic Ethics

Finally, the media’s role in HOM births merits attention. Although journalists provide vital information to society, they may portray an excessively optimistic\textsuperscript{5,12} or critical\textsuperscript{22} picture of multiple births and distort public perceptions. Despite fetal risks in a very-high-multiple pregnancy that rival the risks from other women’s prenatal use of illicit drugs, one review found that only 8% of articles about the Iowa septuplets criticized the parents, whereas addicted persons are usually condemned for subjecting their offspring to similar risks.\textsuperscript{46} Moreover, media curiosity about HOM children after birth can endanger them, as some parents find reporters sneaking onto their property (Ref. 23, p 362) or obtain restraining orders.\textsuperscript{22} Although media attention does not bring wealth,\textsuperscript{20} it does allow families to appeal publicly for help and to thank supporters (Ref. 23, p 361–2). Hospitals can advise parents about risks and benefits of attention from the press and can review privacy rights and potential prejudice (Refs. 16, 22, 23, p 223–4, 361–4). Medical centers can also provide a spokesperson, a telephone number for media inquiries, and security for parental visits to neonatal intensive care unit (Refs. 22, 23, p 223–4).

### Conclusions

Thankfully, most HOM pregnancies have positive outcomes, despite the inherent health, psychosocial, and familial risks. However, with many fetuses in one pregnancy, a series of unfortunate events might transpire, such as MFPR from 5 to 2 fetuses, premature birth of resulting twins, an infant death, and a disabled lone survivor. For both cheerful and challenging scenarios,

### Table 2. Resources About HOMs for Parents and Clinicians

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<tr>
<td>“Patient Information Booklet”: Multiple Pregnancy and Birth: Twins, Triplets and Higher Order Multiples (2004). All available online at <a href="http://www.asrm.org">www.asrm.org</a></td>
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<td>Center for Loss in Multiple Birth (CLIMB): <a href="http://www.climb-support.org">www.climb-support.org</a></td>
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<td>Father2father.com (support for fathers of triplets and more): <a href="http://www.father2father.com">www.father2father.com</a></td>
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<td>Mothers of SuperTwins (MOST): <a href="http://www.mostonline.org">www.mostonline.org</a></td>
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<td>Multiple Births Canada (MBC): <a href="http://www.multiplebirthscanada.org">www.multiplebirthscanada.org</a></td>
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<td>Multiple Births Foundation (MBF): <a href="http://www.multiplebirths.org.uk">www.multiplebirths.org.uk</a></td>
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<td>National Organization of Mothers of Twins Clubs, Inc (NOMOTC): <a href="http://www.nomotc.org">www.nomotc.org</a></td>
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<td>The Triplet Connection (TC): <a href="http://www.tripletconnection.org">www.tripletconnection.org</a></td>
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parents find unbiased information, counseling, and support to be invaluable. Couples’ emotional, ethical, moral, and religious views complicate decisions about fertility treatment, ST, MFM, and withdrawing or withdrawing life support. Thus, parental autonomy, privacy, and choices deserve utmost respect from caregivers. At a societal level, professionals can work to prevent multiples that result from fertility treatments, and can advocate for long-term support of HOM families. It truly takes a village to raise multiple-birth children to their fullest potential.

Acknowledgment

The author thanks Maureen Boyle, Anita Catlin, Pam Chay, Jean Kollantai, and Linda Leonard for topic suggestions, references, and manuscript review.

References