

Multiple pregnancy: a modern epidemic?

The epidemic is subsiding as we improve the delivery of assisted reproductive technology

THE MULTIPLE BIRTH RATE in Victoria rose from 12 to 17 per 1000 pregnancies between 1986 and 1997.¹ There were comparable increases in the United Kingdom and United States. During this period, the rate of all multiple births increased, but the more significant increases were in high-order multiple pregnancies. In Victoria, the triplet pregnancy rate increased more than three-fold from 0.19 to 0.61 per 1000 pregnancies between 1986 and 1998.¹ There was a similar three-fold rise in the rate of triplet pregnancies in the United Kingdom,² while in the United States, the rise was six-fold for triplets and 12-fold for quadruplets.³

These rates of multiple pregnancies peaked at the end of the century and are now slowly falling. There are several reasons why there has been an increase in twin pregnancies and the “epidemic” of high-order multiple pregnancies with low birth rates in the developed world.

Monozygotic twinning

Monozygotic twinning occurs independently of ethnicity, maternal age, parity, nutritional status and environmental factors. It is a random genetic event occurring in 1 in 250 pregnancies. Although the incidence of monozygotic twinning may be doubled after induction of ovulation, and is increased with in-vitro fertilisation for reasons that are yet to be explained, monozygotic twinning has contributed minimally to the global epidemic of multiple pregnancy.^{4,5}

Dizygotic twinning

In developed countries, there was a global decline in dizygotic twinning rates from 1960 until the mid-1970s. Although the exact cause remains unknown, this decline has been attributed to either environmental pollutants or a reduction in sperm quality.⁶ Chronologically, the fall in dizygotic twinning can be attributed to reduced fertility after oral contraceptive pill use became widespread. From the 1980s, the steady increase in dizygotic twinning related to agents that induce ovulation may have masked a true, progressive decline in the spontaneous dizygotic twinning rate.⁶

1: Significant risks associated with twin pregnancies^{1,2,9}

Obstetric complication	Risk*
Anaemia	x2
Pre-eclampsia	x3
Eclampsia	x4
Antepartum haemorrhage	x2
Postpartum haemorrhage	x2
Fetal growth restriction	x3
Preterm delivery	x6
Caesarean section	x2

* Compared with singleton pregnancies

The rate of dizygotic twinning is increased in women aged 35–39 years, with higher parity and tall stature. Rates fall in severely malnourished women. Dizygotic twinning runs in families. If a mother or a sister has dizygotic twins, a woman has double the risk of having dizygotic twins herself. If she has dizygotic twins herself, her risk of having future dizygotic twins is quadrupled.⁷

Folic acid supplementation at the time of conception is widely promoted for reducing the risk of neural tube defects. A systematic review of periconceptual supplementation with folic acid or multivitamins, or both, identified a tendency to an increased risk of twinning (pooled relative risk 1.40; 95% CI, 0.93–2.11).⁸ It is unclear why such an association exists; possibly folic acid improves early fetal survival rather than promoting multiple ovulation.

Assisted reproduction

The most significant cause for the increase in the multiple birth rate in developed countries has been the use of assisted reproductive technology. Inducing ovulation with clomiphene citrate carries an 8% risk of a multiple pregnancy, and with gonadotrophins, a 20% risk. These agents (which act by hyperstimulation of ovarian follicles resulting in one or

more oocytes being released per cycle) are responsible for most high-order multiple pregnancies. Ultrasound monitoring can detect the potential for multiple ovulation in a woman's cycle, and she can be advised accordingly. However, even with ultrasound monitoring, and in the most careful and experienced hands, multiple ovulations can occur.

With in-vitro fertilisation (IVF) and gamete intrafallopian transfer (GIFT), multiple pregnancy rates vary with maternal age and the number of embryos transferred; a 20% multiple pregnancy rate with double embryo transfer and 25% with triple embryo transfer is typical. The increased use of microinjection techniques has seen an increase in monozygotic multiple pregnancies. Improvements in stimulation and laboratory culture techniques have improved embryo quality and, subsequently, the success of IVF and GIFT, particularly in recent years.

Risks of multiple pregnancy

Obstetric complications occur more frequently in multiple pregnancies (Box 1), and perinatal mortality escalates with increasing fetal number. The most recent Victorian figures indicate a perinatal mortality of 9.2 per 1000 pregnancies for singletons, 42.9 per 1000 for twins (first twin 37.8; second twin 47.9), and 145.5 per 1000 for triplets (first triplet 145.5; second triplet 127.3; third triplet 163.6).¹

Preterm delivery is the major cause of adverse outcomes (both short-term and long-term), and is directly related to fetal number (Box 2). The consequences of prematurity (including cerebral palsy, hearing and visual disturbance, behavioural disorders and respiratory disease, among many others) can result in significant social, emotional and financial burdens for families. Costs to the community also increase with the number of infants.

Monochorionic twins have specific risks because they share a placenta. These risks are twin-twin transfusion syndrome, twin reversed arterial perfusion sequence, monoamniocity and conjoined twins. All of these conditions have very significant risks of fetal and neonatal mortality and morbidity.

The risks associated with being born in a multiple pregnancy do not end with delivery. Apart from the consequences of prematurity, or the morbidity associated with monochorionicity, children born as twins or in higher order multiple pregnancies have increased rates of neonatal death, speech and reading difficulties, and behavioural disorders including attention deficit hyperactivity disorder.

Twins have a four-fold, and triplets a 20-fold, increase in cerebral palsy compared with singletons. If a twin develops cerebral palsy, the risk of its co-twin developing cerebral palsy is 12%. Death of a co-twin increases the risk of cerebral palsy for the survivor to around 5% with the risk rising to 40% with monochorionicity.^{10,11}

Preventing multiple pregnancy

All women undergoing ovulation induction should be offered monitoring of follicular development. They should be fully advised of the potential for a multiple pregnancy, and should be made aware of the consequences of pursuing a conception when multiple follicles are present.

2: Rates of preterm delivery by fetal number¹

Number of fetuses	Delivery	
	<28 weeks	<37 weeks
Singleton	0.7%	6.2%
Twins	4.4%	52.1%
Triplets	21.8%	98.2%

It is axiomatic that the fewer the number of embryos transferred after IVF, the lower the risk of a multiple pregnancy. It has been recent practice to offer women the transfer of only two embryos to optimise the chance of pregnancy without significantly increasing the risks of a multiple pregnancy. This practice also helps reduce the costs to the patient associated with repeated embryo transfers. However, with the continuing improvement in pregnancy rates with IVF, single embryo transfer should now be considered by all women, particularly those who are younger and those who already have children.

Multifetal pregnancy reduction (MFPR) by intracardiac potassium chloride injection to reduce the number of "excess" fetuses is often seen as the answer to reducing the risks and avoiding the complications of high-order multiple pregnancy. Notwithstanding the social, moral and ethical issues associated with this technique, there are significant risks to the remaining fetuses associated with the procedure. For example, MFPR from a triplet to a twin pregnancy is associated with an 8% risk of miscarriage of the remaining twins. However, the procedure offers a marginal reduction in perinatal mortality and reduces the handicap rate from 1.5% to 0.6% per fetus.¹²

Conclusions

Multiple pregnancy usually has a satisfactory outcome, culminating in the birth and development of healthy children, often long awaited, and much loved by their parents. However, the consequences of some multiple pregnancies for the parents, the children and the community remain significant. Multiple pregnancies reached epidemic proportions in the late 1990s as a consequence of assisted reproductive technology. The rate is now falling and this trend should continue as practitioners respond with careful monitoring of ovulation induction and with reduced numbers of embryos transferred after IVF.

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