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Deciding how many embryos to transfer: ongoing challenges and dilemmas

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Abstract Despite the risks associated with twin and higher-order multiple births, and calls in many countries for single-embryo transfer as the standard of care for good-prognosis patients, providers frequently transfer additional embryos, raising critical questions as to why this is the case and what can be done about it. In-depth interviews of approximately 1 h each were conducted with 27 IVF providers (17 physicians and 10 other healthcare providers) and 10 patients. Professional guidelines often contain flexibility and ambiguities or are unenforced. Thus, both providers and patients frequently wrestle with several dilemmas. Decisions about the number of embryos to transfer emerge as dyadic, dynamic and affected by several factors (e.g., providers' type of institution, and personal and professional experiences and perceptions of the data), leading to differences in whether, how and with what effectiveness clinicians address these issues with patients. Many clinicians feel that the evidence concerning the apparent increased risk associated with a twin birth is not 'compelling', and patients frequently minimize the hazards. These data, the first to explore several critical aspects of how providers and patients view and make decisions about the number of embryos to transfer, thus highlight tensions, uncertainties and challenges that providers and patients confront, and have key implications for future practice, research, policy and education.



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Despite the risks associated with twin and other higher-order multiple births, and subsequent calls for single-embryo transfer (SET) as the standard of care for good-prognosis patients, most providers transfer additional embryos, raising critical questions as to why this is the case. As a consequence

of assisted reproduction via IVF, rates of twin and other higher-order multiple births have increased over recent years, essentially doubling between the mid-1970s and 2011 in many developed countries, including the UK, France, Germany, the USA and South Korea ([Osterman et al., 2015](#);

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Pison et al., 2015). Critics have decried an 'epidemic' of multiple births (Muir, 2001), and the case of 'Octomom' in the USA – in which a woman on federal assistance gave birth to octuplets following treatment with artificial reproductive technologies – brought world-wide attention to this issue (Davidson, 2010).

When transferring more than one embryo, the rate of complications increases. Among infants born to mothers through IVF, twins are 12 times more likely than singletons to be born prematurely, 16 times more likely to have low birth weight, and about five times more likely to have respiratory complications or jaundice (Sazonova et al., 2013). Mothers of twins are about two and a half times more likely than those of singletons to have pre-eclampsia, over eight times more likely to have premature pre-term rupture of membranes, and four times more likely to require a Caesarean section (Sazonova et al., 2013). Although some providers and patients may see twins as a means of saving money, the overall cost per live birth (for both mothers and infants) for one double-embryo transfer (DET), rather than two SET, until 6 months of age, are roughly equal, given neo-natal intensive-care unit (NICU) and other expenses (Thurin-Kjellberg et al., 2006). Over time, twins can cost even more, given the associated long-term complications (Collins, 2007; Wølner-Hanssen and Rydhstroem, 1998).

Opponents of establishing SET as the standard of care for good-prognosis patients argue that twins are desirable, and that the reported risks are exaggerated (Gleicher and Barad, 2009). A meta-analysis of studies published from 1995–2008 (Baruffi et al., 2009) found that DET had about twice the pregnancy and birth rate of SET. Yet over the past decade, since many of these studies were conducted, SET success has increased substantially, while higher complications with DET continue. A more recent meta-analysis (McLernon et al., 2010) found that the birth rate from a fresh SET followed by a frozen SET was not significantly different than that of one fresh DET (38% versus 42%), and that the risks of a preterm birth were five times higher for DET than for SET. One Italian centre recently suggested that twin pregnancies compared with singleton pregnancies had 31.8 times the rate of perinatal complications (La Sala et al., 2016). Other data show that for women over 40, transferring three, rather than two embryos does not increase the live birth rate (Lawlor and Nelson, 2012).

Therefore, as SET success rates continue to rise, commentators have increasingly argued that SET should become the standard of care (Kissin et al., 2015), and that this may be achievable through altering insurance reimbursement, providing appropriate educational materials and including patients' partners in discussions of risk (Griffin et al., 2012; Hope and Rombauts, 2010; Leese and Denton, 2010).

In recent years, guidelines in various countries have thus sought to reduce the number of embryos transferred, including the UK (HFEA, 2013), Australia/New Zealand (Norman, 2016), and Canada (Canadian Fertility and Andrology Society, 2006). The number of countries that limit the number of embryos to be transferred has been steadily increasing, and in 2013 was around 17 (Stillman et al., 2013). In the UK, the Human Fertilization and Embryology Authority (HFEA) has progressively lowered the maximum multiple birth rate from 24% in 2009/2010, to 15% in

2010 and 10% in 2012 (HFEA, 2013). Belgium coupled reimbursement for assisted reproductive technologies to a restriction in the number of embryos transferred and reduced the multiple pregnancy rate from 27% in 2003 to 11% in 2010 (De Neubourg et al., 2014). However, many countries still allow considerable room for physician discretion. The American Society of Reproductive Medicine (ASRM), for instance, states that 'physicians should be encouraged to counsel good-prognosis patients to accept' SET; and highlights the importance of clinical judgement in selecting the best candidates (The Practice Committee of the ASRM, 2012). For patients <35 years of age with a favourable prognosis, 'providers should only transfer a single embryo, and not more than two embryos' (The Practice Committee of the ASRM and the Practice Committee of the SART, 2013). For patients aged 38-40, and 41-42, ASRM states that no more than three and five cleavage-stage embryos, respectively, should be transferred. Patients, who have failed two or more IVF cycles or have a less favourable prognosis, can receive an additional embryo. For patients aged over 43, there is no limit (The Practice Committee of the ASRM and the Practice Committee of the SART, 2013).

Since 1998, the rate of twin and multiple births have begun to decrease – as providers have begun to transfer three or more embryos less frequently (Kulkarni et al., 2013) – but remain higher in numerous countries than many observers argue is optimal. Thus, 17% of all Canadian births were twins in 2013 (Canadian Fertility and Andrology Society, 2006), and multiples accounted for approximately 17% of British pregnancies (HFEA, 2013) and 19.4% of all births in Europe in 2011 (Kupka et al., 2016). Among cycles using IVF and intra-cytoplasmic sperm injection (ICSI), transfers of three and four embryos accounted, respectively, for 14.5% and 1.3% in Europe as a whole, including 49.4% and 9.9% in Greece, 34.6% and 4.5% in Italy, 26.2% and 3.1% in Hungary, and 40.7% and 7.9% in Bulgaria (Kupka et al., 2016). Twin and triplet deliveries accounted for 18.6% and 0.6% of assisted reproductive technology births using IVF and ICSI in Europe as a whole, including, 41.5% and 3.5% in Greece, 28.2% and 1.7% in Romania, 22.0% and 6.5% in Moldova, and 26.5% and 5% in Serbia (Kupka et al., 2016). The most recent summary data available from the Society for Assisted Reproductive Technologies (SART) from 2013, suggests that among all transfers using fresh non-donor eggs or embryos, 76.4% involved one or more embryos and 20.7% involved three or more embryos; and the average number of fresh and thawed embryos from non-donor eggs transferred in women under 35 was 1.8% and 1.7%, respectively (Centers for Disease Control and Prevention, 2013). Among live births from fresh embryos, for mothers under 35 and aged 35-37, respectively, 28.3% and 25.5% of US births were twins and approximately 1% were triplets or higher-order multiples. *The SART Clinic Summary Report (2016)* lists the percentage of cycles, retrievals and transfers resulting in live births, but does not separate these data by the number of embryos transferred (1 versus 2 or more). The success rates would presumably be lower for singletons (versus twins).

A few studies have suggested that physicians may fail to follow SET because of patient requests. A literature review revealed that most patients prefer twins rather than singletons (Leese and Denton, 2010). In one study, 52% of

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