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Infant outcomes of assisted reproduction

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ABSTRACT

Assisted reproductive technologies (ART) have become widely used in the treatment of subfertility over the last 30 years. Currently 1.7% of all births in the UK occur after assisted conception. This review summarises work that has been undertaken to investigate health outcomes of these children and summarises areas where uncertainty continues to exist. Much of the adverse health outcomes of children born after ART are related to higher order birth; however evidence suggests adverse perinatal outcomes in singletons as well as twins and triplets. The cause of adverse health outcomes in ART conceived children is as yet unclear and studies investigating causal factors such as underlying subfertility are discussed.

1. Introduction

The number and proportion of children born after assisted conception are increasing. There have already been over 3,500,000 births after Assisted Reproductive Technologies (ART) worldwide and with falling fertility rates in some countries this is likely to rise [1]. 1.7% of all children born in the UK in 2006 were conceived after ART, compared to 0.5% in 1992 [2].

Assisted reproductive techniques have developed rapidly since the birth of the first IVF conceived infant, Louise Brown, in 1978. The diverse range of techniques available includes gamete intra-fallopian tube transfer (GIFT), oocyte donation, embryo cryopreservation techniques, intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis (PGD) and blastocyst culture (extended embryo culture) as well as standard IVF.

Whilst the development and use of these techniques have progressed rapidly, the same cannot be said for research into the safety outcomes of such treatments. The reason for this is not clear; however a contributing factor may be that institutions which provide ART are not usually responsible for providing care in pregnancy. Therefore they often have little direct contact with the family after the initial treatment period, making follow-up data difficult to collect. In addition some of the potential adverse outcomes are rare events and therefore very large cohorts are required. Currently there are no surveillance systems specifically developed for studying outcomes of ART and thus research has generally used registries and databases set up for other purposes. This often results in essential data not being available, such as information on confounding factors [3].

Despite these problems there is an emerging literature reporting infant outcomes of ART. Some of these outcomes have been studied empirically and some as the result of theoretical concerns and animal models. Potential risks of ART include multiple births, low birth weight and prematurity in singleton births, congenital abnormalities, imprinting disorders, neurodevelopmental risks, childhood cancers and growth disorders. This review aims to present much of this data including positive and negative outcomes, in the context of the methodology difficulties of many of the studies.

2. Perinatal outcomes

2.1. Multiple births

The most well documented risk of ART is multiple births. Assisted conceptions account for 21% of all multiple births in the UK although they only account for 1.7% of all births (Table 1).

The majority of multiple ART births are dizygotic twins, resulting from multiple embryo transfer. However interestingly there are also higher rates of monozygotic twins in ART pregnancies (1–5% of all ART pregnancies compared to 0.4% in the general population) [4,5]. Assisted hatching and blastocyst culture appear to be particular risk factors for monozygosity. This is thought to be due to potential manipulation of the zona pellucida [6,7].

Multiple pregnancies in general are associated with several adverse outcomes including preterm birth, low birth weight, neonatal mortality, congenital malformations and disability amongst survivors. [8] Delivery before 37 weeks, for example, was reported to occur in 44% of all twin pregnancies compared to in 6% of all singleton pregnancies. [9] Twins have a 6 fold increased risk of mortality compared to singletons. [9] They also have a high risk of morbidity, predominantly associated with preterm birth, resulting in a 1 in 13 risk of permanent handicap in twins. [10].

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Table 1
ART births in the UK 2006. (Table complied from HFEA data [2]).

All ART live births	All births		Singletons		Twins		Triplets and higher order		All multiple births	
	Births	Babies	Births	Babies	Births	Babies	Births	Babies	Births	Babies
Number	10,697	13,085	8346	8346	2315	4630	36	109	2351	4739
As a % of all ART births	100%	100%	78%	64%	22%	35%	0.3%	0.8%	**22%**	**36%**
As a % of all UK births of that type	1.45%	1.75%	1.2%	1.2%	21%	21%	24%	24%	**21%**	**21%**

2.1.1. Single embryo transfer

To reduce these risks practitioners and researchers alike have sought to reduce the rate of multiple births after ART [11,12]. Transferring a maximum of two embryos per cycle is now an accepted practice in the UK and the rate of multiple births has decreased as a result [2]. However, single embryo transfer further reduces the rate of multiple births [12,13]. A recently updated Cochrane review reported that a single embryo transfer (SET) followed by transfer of a cryopreserved embryo in a subsequent cycle, resulted in a similar live birth rate to a double embryo transfer (DET) (Odds Ratio = 0.81%, 95% CI = 0.59–1.11). A significantly lowered multiple birth rate for SET compared to the DET was also reported (OR = 0.04, 95% CI = 0.01–0.11). [12] A Scandinavian RCT showed SET to be cost effective and improve neonatal outcome with significantly less preterm births and significantly lower numbers of low birth weight infants compared to conceptions using DET [14].

Although there are clearly serious and commonly occurring risks to ART multiple births, it is unclear if perinatal outcome is better or worse compared with similar high order spontaneously conceived pregnancies. Hansen et al.'s recently published linkage study reported that ART conceived twins had a higher risk of adverse perinatal outcome including low birth weight, preterm birth and perinatal mortality compared to spontaneously conceived twins [15]. However a meta-analysis published in 2004 showed no significant difference in perinatal outcome between ART multiple births and spontaneously conceived high order births [16].

2.2. Singleton perinatal outcome

Data from recent meta-analyses suggests that singletons conceived after ART have significantly higher rates of the following when compared to spontaneously conceived singletons (after adjustments for maternal age and parity) (Table 2):

- Preterm delivery (<37 weeks)
- Low birth weight (<2500 g)
- Very low birth weight (<1500 g)
- Infants who are small for gestational age [16–18]
- Perinatal mortality

These results were echoed by an Irish study, which in addition showed an increased incidence of placenta previa in ART singleton pregnancies [19]. Despite this evidence there are limitations to these studies. It is impossible to blind practitioners in individual studies thus it could be argued that ART pregnancies might be managed differently than spontaneously conceived pregnancies. For example there may be a lower threshold to deliver ART pregnancies resulting in iatrogenic preterm delivery and low birth weight [17]. However some adverse outcomes such as perinatal mortality, very low birth weight and being small for gestational age, are unlikely to be affected by iatrogenic influences. The fact that such outcomes are also significantly more likely in ART pregnancies suggests differences are not explained by treatment bias alone. Another potential explanation is that some of these singleton births may be multiple pregnancies in the first trimester and undergo early fetal loss. Indeed there is evidence to suggest that early fetal loss may result in adverse perinatal outcome for both singletons and twins [20,21]. Luke et al. studied over 22,000 singleton births and 9000 twin births after ART. They found that the 1727 singleton pregnancies with two or three fetal heartbeats detected in the first trimester and the 559 twin pregnancies with three fetal heartbeats detected in the first trimester resulted in offspring who were significantly more likely to be preterm and low birth weight compared to similar order ART pregnancies which did not suffer early fetal loss [20,21]. However in the largest single study on perinatal outcome of singletons conceived after ART, risk ratios continued to be significantly elevated after restriction to pregnancies with one fetal heart in the first trimester [3]. This study also analysed outcome according to the length of culture and found no difference between infants born after transfer of an embryo cultured for three days and those born after extended culture (five days, also known as blastocyst culture) [3].

2.2.1. Adverse perinatal outcomes: subfertility or assisted reproduction?

Whether adverse outcomes in ART conceived children are caused by assisted reproductive technologies themselves, underlying subfertility or by a combination of these is a key question in ART outcome research. Romundstad et al. attempted to address this question with regard to adverse perinatal outcome in singletons by using data from population based registries to compare children born after ART with their spontaneously conceived siblings ($n = 2204$ per group) [22]. When the groups as a whole were compared (i.e. all assisted conception vs. all spontaneously conceived) the assisted conception

Table 2
Adverse perinatal outcomes in ART conceived singletons compared to naturally conceived singletons.

	Adverse perinatal outcomes— ART singletons compared with spontaneously conceived singletons					
	Number of ART conceived infants	Preterm birth (<37 weeks gestation)	Low birth weight (<2500 g)	Very low birth weight (<1500 g)	Small for gestational age	Perinatal mortality
Jackson et al. 2004 [17] Meta-analysis	12,283	OR-2.0 (95% CI 1.7–2.2)	OR-1.8 (95% CI 1.4–2.2)	OR-2.7 (95% CI 2.3–3.1)	OR-1.6 (95% CI 1.3–2.0)	OR-2.2 (95% CI 1.6–3.0)
Helmerhorst et al. 2004 [16] Meta-analysis	5361	RR- 3.0 (95% CI 2.1–4.3)	RR-1.4 (95% CI 1.2–1.7)	RR-3.0 (95% CI 2.1–4.4)	RR- 1.5 (95% CI 1.4–1.7)	RR-1.7 (95% CI 1.1–2.5)
McDonald et al. 2005 [18] Meta-analysis	Not available	OR- 1.9 (95% CI 1.4–2.7)	N/A	OR-3.8 (95% CI 4.3–5.8)	OR-1.6 (95% CI 1.2–2.1)	OR-2.4 (95% CI 1.5–5.8)
Schieve et al. 2004 [3][a] Large US register based study	62 551	RR-1.4 (95% CI 1.3–1.5)	RR-1.6 (95% CI 1.5–1.8)	RR-1.8 (95% CI 1.5–1.9)	N/A	N/A

[a] Included as large cohort used.