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The impact of cross-border IVF on maternal and neonatal outcomes in multiple pregnancies: Experience from a UK fetal medicine service



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ABSTRACT

Objectives: To determine whether women seeking NHS care for IVF multiple pregnancies were more likely to have sought IVF treatment overseas and whether this was associated with different maternal and neonatal outcomes.

Study design: A single large tertiary centre, for perinatal care in northwest London. Sixty-five women were referred to our fetal medicine centre, between 2012–2016, with IVF conceived multiple pregnancies. Inclusion criteria: In Vitro fertilisation and conception of twins/ triplets/quadruplets. Exclusion criteria: Intra-uterine insemination, ovulation induction, Clomid-conception and singleton pregnancies. The primary outcome measure was the Country where IVF treatment was performed. The secondary outcomes measures included the specifics of IVF treatment (e.g. number of embryos transferred), subsequent pregnancy outcomes (e.g. live-births and prematurity) and neonatal outcomes (e.g. length and cost of care).

Results and Conclusion: Thirty-eight women had IVF overseas; they were older and had more pre-existing medical conditions. Eleven pregnancies used donor embryos, of which ten were from overseas treatment. 75% of women treated overseas conceived a triplet or higher order pregnancy compared to fewer than 10% of women who conceived in the UK. Almost half of all women treated overseas had more than two embryos transferred.

Overseas IVF pregnancies had poorer obstetric and neonatal outcomes: 24% of live born babies died in the neonatal period compared to 0% in the UK group.

The average neonatal costs per baby born from overseas IVF were £20, 600: two-and-a-half times higher than for those whose mothers conceived in the UK.

Higher order multiple pregnancies are greatly over-represented by those undergoing IVF in overseas clinics. These are associated with poorer obstetric and neonatal outcomes. Perhaps paradoxically, improving NHS provision of fertility services might improve outcomes for the mother and babies while reducing the long-term burden to both fertility patients and the NHS.

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Introduction

In the UK 1 in 7 couples may experience infertility [1]. With the advent of treatments such as in vitro fertilisation (IVF) many couples now have a viable route to seek a cure for childlessness. As artificial reproductive technologies (ART) have advanced, so have

their success rates. However, IVF is not without risk, most commonly as a result of multiple pregnancies [2,3]. Prior to the widespread availability of ART the rate of triplet conception in the UK was 1 in every 9260 pregnancies, yet in 2008 almost 1 in 4 IVF pregnancies were multiples [4].

Multiple pregnancies are associated with higher maternal morbidity and neonatal morbidity and mortality, mostly secondary to complications associated with prematurity [3]. In addition, estimates suggest multiple pregnancies cost the NHS an additional £4127.00 per pregnancy [5]. This may be due to the additional antenatal appointments and scans required during the course of a multiple pregnancy [6].

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In response to the 2008 findings, the Human Fertility and Embryology Authority (HFEA) launched the “One at a time” campaign with the aim of reducing the multiple pregnancy rates to 10% of all ART births in the United Kingdom [7]. The most recent HFEA code of practice recommended limiting embryo transfers to a single embryo in women less than 40 years and no more than three embryos in women over 40 years [8].

Despite the UK HFEA policy, multiple pregnancies are still commonly seen in NHS clinics, possibly as a result of fertility treatment overseas [9], where the single or limited embryo transfer policies do not apply. This phenomenon of travelling for fertility treatment has been coined ‘cross-border reproductive care’ (CRBC) by the European society of human reproduction and endocrinology (ESHRE) [10]. The aim of this study was to determine whether women seeking NHS treatment for multiple IVF pregnancies were more likely to have sought CRBC and whether these women and babies had higher rates of adverse outcomes.

Methods

This observational study was performed in a single tertiary centre for fetal and neonatal medicine in the UK. The details of all women seeking NHS care following fertility treatment, and the outcomes of these pregnancies, are available using specific databases for the purpose of audit and quality improvement; computerised ultrasound and fetal medicine database (Astraia GMBH, Munich), computerised patient notes (Cerner, Kansas City USA), and ultrasound records (Astraia GMBH, Munich) were analysed for each patient. Neonatal information was extracted using the hospital database (Badger Net, Clevermed, UK).

The appropriate databases were retrospectively interrogated for women who had multiple pregnancies following IVF treatment between 2012 and 2016. A multiple pregnancy was defined as a twin, triplet and quadruplet pregnancy and included all variations of chorionicity. The following data were extracted: location of fertility treatment (UK or overseas), the use of donor gametes, number of embryos transferred, number of fetuses lost to viability, fetocide and the timing of these losses, median gestation at delivery, neonatal unit admissions, and the number of babies who survived to discharge.

Where data regarding fertility treatment were missing, patients were included but data was analysed separately to those where location of IVF was known.

Economic analysis was performed to establish the cost of admissions to the neonatal unit. The British Association of Perinatal Medicine (BAPM) categories of care 2011 report was used to define levels of neonatal care: neonatal intensive care (NICU), high dependency unit (HDU), special care baby unit (SCBU), or postnatal/transitional care (PN). Associated financial costs were assigned using cost codes from the hospital business report.

Descriptive data was analysed using Microsoft Excel 2010.

Patient and public involvement

There was no patient or public involvement in the design of this review.

Results

During the study period, 65 patients with IVF multiple pregnancies were identified. 38 had IVF in the UK, 22 overseas and five patients had no data recorded regarding location of treatment (Table 1). Overseas IVF was performed in India, Spain, Nigeria, USA, Jordan, Lebanon, Cyprus, Denmark, Russia, and Bulgaria. Women treated overseas were older compared to those in the UK (median 40 years versus 34.5 years, respectively). The most common multiple pregnancy was a twin pregnancy, and only one patient had a quadruplet pregnancy.

Twin pregnancies conceived in the UK had a higher rate of double embryo transfer (DET) and lower triple embryo transfer (TET) than overseas IVF pregnancies (Table 2). The average gestation at delivery for twin pregnancies in both groups were similar but those undergoing IVF in the UK had a slightly higher number of babies taken home as a percentage of those expected from the first trimester scans (92% vs. 86%) (Table 2).

Triplet and quadruplet pregnancies conceived overseas were more likely to have had a triple/quadruple embryo transfer; 88% had more than two embryos transferred compared to 25% treated in the UK. Although both groups delivered prematurely, the average gestation at delivery was lower for women who had overseas IVF (31 vs. 34+5 weeks) (Table 2).

Women, who had IVF overseas, experienced a poorer pregnancy outcome in terms of prematurity and neonatal deaths (Table 1). Their babies had a higher rate of neonatal admission (31%) compared to the UK group (18%) and a longer average stay in all levels of the neonatal unit (Table 3). Subsequently, neonatal costs

Table 1
Background demographic characteristics.

	UK	Overseas	Undisclosed location
Total No. Patients	38	22*	5
Maternal age (Median, range) years	34.5 (23–45)	40 (26–56)	36 (29–44)
Parity (Mode, range)	0 (0–9)	0 (0–3)	0 (0)
Twins (total = 53)	34	14	5
Triplets (total = 11)	4	7	0
Quadruplets (total = 1)	0	1	0
Donor gametes used (No. Pregnancies)	0	10	1
No. Losses to viability	3	3	2
Fetocide	2	2	0
N* 3 rd trimester losses	3	0	0
Median gestation at delivery, weeks (range)	34+5 (30+6–38+1)	32+5 (23–39+1)	34+5 (34–36)
No. babies expected from dating scans	70	53	10
No. babies lost to follow-up/delivered elsewhere	7	3	0
No. live births	65	45	8
Babies live born as % expected at start of pregnancy	92% (65/70)	85% (45/53)	80% (8/10)
Babies ‘taken home’ as % of those expected from dating scan	92% (65/70)	75% (40/53)	80% (8/10)

* Among the Overseas group, two patients were missing embryo transfer data.

Table 2

Outcome in relation to number of embryos transferred and fetus number: UK vs Overseas IVF multiple pregnancies.

Multiple order type (twins/higher)	UK		Overseas		Undisclosed location
	Twins (n = 34)	Higher order (n = 4)	Twins (n = 14)	Higher order (n = 7)	Twins (n = 5)
Median maternal age (range) years	35 (23–42)	36 (32–45)	40 (26–56)	41 (32–52)	36 (29–44)
% Single embryo transfers (SET)	21% (7/34)	0	43% (6/14)	0	Undisclosed
% Double embryo transfers (DET)	76% (26/34)	75% (3/4)	43% (6/14)	0	Undisclosed
% Triple or quadruple embryo transfers	3% (1/34)	25% (1/4)	14% (2/14)	88% (7/8)	Undisclosed
Median gestation at delivery, weeks (range)	36 (30+6–38+1)	34+5 (31–39)	36 (30+3–38)	31 (23–36+6)	34+5 (34–36)
Neonatal Deaths	0	0	0	5	0
Babies 'taken home' as % of those expected from dating scan	92% (59/64)**	67% (6/9)***	86% (24/28)****	68% (13/19)*****	80% (8/10)*****

* One patient out of the eight did not know the number of embryos transferred.

** 1 loss pre-viability, 1 fetocide, 3 stillborn.

*** 1 loss pre viability; 1fetocide; 1Stillborn.

**** 3 losses pre viability, 1fetocide.

***** 1fetocide, 5 neonatal deaths.

***** 2 losses pre viability.

Table 3

The neonatal cost.

	UK	Overseas	Undisclosed location
Median days in NICU (total)	8 (32)	43(298)	0
Cost per day / per baby £1260			
Median days in HDU (total)	7(72)	13(174)	2 (5)
Cost per day / per baby £925			
Median days in SCBU (total)	16 (147)	23(373)	5 (26)
Cost per day / per baby £550			
Median days in PN/transitional (total)	5 (228)	5(148)	4 (29)
Cost per day / per baby £310			
Total cost of NICU	£40,320.00	£375,480.00	0
Total cost of HDU	£66,660.00	£160,950.00	£4625.00
Total cost of SCBU	£80,850	£205,150.00	£14,300.00
Total cost of PN/transitional	£70,060	£45,880.00	£8990.00
Cost per group	£258,450.00	£787,460.00	£27,915.00
Average cost per baby admitted to NICU/HDU/SCBU (not PN ward)	£7826.25	£20,599.44	£2365.63
Total cost of all babies admitted	£1,073,825.00		

were greater, accounting for 73% of total neonatal expenditure (Table 3).

Pre-existing medical conditions were present in 32% of women who had IVF overseas and 5% in women treated in the UK (Table 4). 57% of women with a pre-existing medical pathology, who had IVF overseas, were over the age of 40 years. Despite pre-existing maternal morbidity and advanced age, a single pregnancy lost a pre-viable twin and all live born babies survived to be discharged.

Medical and/or obstetric complications developed in 28% of all IVF multiple pregnancies; there was little difference for those undergoing IVF in the UK compared to overseas. These conditions and complications ranged from gestational diabetes and pre-eclampsia to post-partum haemorrhage requiring hysterectomy (Table 4). Within this group of women with medical and/or obstetric complications, there was a single pre-viable loss of a triplet and all live-born neonates survived to discharge.

Discussion

We report that twin IVF pregnancies were most likely to have been conceived in the UK, but most higher order multiple pregnancies had treatment overseas with donor embryos. All women who had a triple embryos transfer in the UK were over 40 years and used autologous oocytes. In contrast 56% of women who

had a triple/quadruple embryo transfer overseas were under the age of 40yrs, and 45% used donor embryos. The HFEA advises no more than two embryos are transferred in women using donor embryos regardless of age [8]. Despite concerns that a reduction in the number of embryos transferred would negatively impact the overall IVF pregnancy rate; this has not occurred in the UK. The rate of elective single embryo transfers (eSETs) increased from 5% (2008) to 29% (2014), with stable pregnancy rates and a corresponding reduction in multiple gestation IVF pregnancies from 27% (2008) to 11% (2016) [2]. Our findings suggest that overseas clinics do not follow similar practices to reduce multiple pregnancies

Lack of access to donor embryos in the UK may also influence the decision for CRBC. All women who conceived with donor embryos had IVF overseas (with the exception of one patient who did not disclose location). They had poorer neonatal outcomes compared to autologous gamete pregnancies: lower average gestation of delivery (33+5 vs. 35+5 weeks) and all of the neonatal deaths. They accounted for 65% of total neonatal costs. We acknowledge the difficulty women have in accessing donor gametes, which could be addressed by the development of more oocyte donor programmes in the UK.

As suspected, it is highly likely women seek CRBC because they fail the 'age eligibility' criteria for IVF on the NHS: of women who

Table 4
Obstetric and pre-existing medical pathology.

Women with pre-existing medical condition	UK (5%; 2/38)	Overseas (32%; 7/22)
Median age (years)	38.5	43
Medical conditions	<ul style="list-style-type: none"> • Inflammatory arthritis • Hyper-prolactinaemia 	<ul style="list-style-type: none"> • Hepatitis C • Epilepsy • Paroxysmal atrial fibrillation • Type 2 diabetes mellitus • Chronic renal disorder • Mental health (history of drug abuse)
Median gestation at delivery (weeks)	36	34+6
Admission to neonatal unit (% of those live born)	38% (5/13)	0
Overall babies taken home as % of expected (number confirmed in early pregnancy)	93% (13/14)	
Developed obstetric complications	UK (32%; 12/38)	Overseas (23%; 5/22)
Obstetric complications	<ul style="list-style-type: none"> • Pre-eclampsia • Pregnancy induced hypertension • Gestational diabetes • Obstetric cholestasis 	<ul style="list-style-type: none"> • Pre-eclampsia • Obstetric Cholestasis • Massive obstetric haemorrhage
Median age	33	40
Median gestation at delivery (weeks)	36+2	34
Admission to neonatal unit (% of those live born)	25% (6/24)	55% (6/11)
Overall babies taken home as % of expected (number confirmed in early pregnancy)	97% (37/38)	

had IVF overseas, half were aged over 40 and the oldest was 56 years old. Obstetric risks in women seeking CRBC were further increased due to pre-existing medical pathologies; all but two women with pre-existing medical co-morbidities had IVF overseas. Their conditions may not have prohibited fertility treatment in the UK, but they are likely to have had more explicit counselling regarding the risks and earlier access to high-risk obstetric clinics prenatally. Possibly indicative of the high level of antenatal and fetal medicine care afforded to NHS patients, the survival of babies born to mothers with medical co-morbidities was 93%.

Regardless of clear NICE guidance on the provision of IVF [5], many women are not receiving appropriate access to fertility treatment. Fertility services have borne the brunt of disinvestment strategies. In 2017, 3.4% of clinical commissioning groups (CCGs) had ceased NHS funded IVF treatment with an additional 7% entertaining the idea of reducing or stopping services altogether [11]. The Fertility Fairness charity audited all UK CCGs and found that only 12% offer the NICE recommended number of cycles in 2017 compared to almost double that in 2013 [11]. This can be prohibitively expensive, the average cost to a CCG of an IVF cycle is £3483.00 [11] and private IVF cycles have a huge range in cost with the average cycle costing £5000 [12]. Thus infertile couples not unreasonably, explore opportunities with overseas clinics who may offer competitive pricing, but where HFEA guidance does not apply.

Based on a single large perinatal centre's experience, we find that the long-term costs of not offering carefully regulated treatment may be higher to the NHS in terms of higher maternal complications and neonatal costs. This has been demonstrated in Quebec, where, after the introduction of full public funding for IVF [13], there was a significant decrease in IVF multiple pregnancy rates (29.4%–6.4%) and improved economic efficiency (cost per live birth reduced from \$49,517.00 to \$43,362.00).

Conclusion

Overseas IVF is very common in women with higher order multiple pregnancies; these women are older, have more medical co-morbidities and suffer worse obstetric and neonatal outcomes. An environment not conducive to IVF funding most likely leaves women who are at higher risk of adverse pregnancy outcomes feeling there is no choice but to travel abroad for treatment, where the likelihood of multiple embryo transfers is greater and associated with worse outcomes and higher costs. Paradoxically, improving NHS provision of fertility services might improve outcomes for the mother and babies, while reducing the long-term burden to both patients and the NHS.

Limitations

The veracity of the data we obtained was reliant on clinician documentation or patient disclosure of the details of fertility treatment. Therefore it is very likely that we have underestimated the number of pregnancies associated with non-UK IVF treatment. This project involved a single tertiary referral centre for fetal medicine in London which may not be indicative of what is happening within the UK overall. Nevertheless, this data has value, as it is apparent that there is no robust way of collecting this information, and the findings that we present may be relevant in informing resource allocation for fertility treatments within the NHS.

Contribution to authorship and authorship agreement

CL and RS formulated the idea of the review. RJ, JB, RS and CL contributed to the researching and writing of the review. JD gave advice on the manuscript, analysis and regulatory aspects. TP accessed and analysed the database, and reviewed the manuscript. All authors approved the final article.

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Details of ethics approval

This review was registered as an audit within Imperial College NHS Healthcare Trust audit department. All data was collected retrospectively and fully anonymised for the analysis. No ethical approval was required.

Data sharing statement

Additional data is available by emailing Christoph.lees@imperial.nhs.uk

Disclosure of interests

JD is on the NICE guideline committee for the update of Twins and Triplets Guideline,

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