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Research article

Towards a better understanding of preimplantation genetic screening and cumulative reproductive outcome: transfer strategy, diagnostic accuracy and cost-effectiveness

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Abstract: A decision model was constructed to compare genetic testing and not testing, for the transfer of all suitable embryos, one at a time, from a cycle with up to ten embryos, until a first live birth was achieved or there were no more embryos available (a full cycle). Two strategies were investigated: (i) a fresh transfer with subsequent serial warmed cryopreserved embryo replacement, and (ii) freeze-all prior to serial embryo replacement. Sensitivity analyses were performed to assess the effect of embryo warming survival and diagnostic accuracy on cumulative rates. Cost-effectiveness was assessed using the incremental cost-effectiveness ratio for a live birth event, and a clinical miscarriage avoided. Reproductive outcome probabilities were obtained from published prospective non-selection studies, and costs from websites and publications.

Given 100% embryo warming survival and no false abnormal genetic test results, the live birth rate for a full cycle was the same with and without testing for both transfer strategies. Compared to not testing, it was theoretically possible for testing to be favoured for live birth only for the fresh and frozen transfer strategy, where more than one embryo was available, and dependent on the efficiency of warming survival and the positive predictive value of the test; however, this was unlikely to be cost-effective from a society perspective without a substantial reduction in genetic testing costs. For both transfer strategies, when more than one embryo was available, testing was more likely to achieve a live birth event following the first attempt with fewer attempts required overall. Testing was likely to be effective to avoid a clinical miscarriage but also to be expensive from a society perspective compared to the cost of dilation and curettage.

Keywords: Embryo selection; preimplantation genetic diagnosis; aneuploidy screening; cost-effectiveness; diagnostic accuracy

Abbreviations

AT	aneuploidy test
CLBR	cumulative live birth rate
CVS	chorionic villus sampling
D&C	dilation and curettage
FET	frozen embryo transfer
ICER	incremental cost-effectiveness ratio
ICSI	intracytoplasmic sperm injection
IVF	in vitro fertilization
mtDNA	mitochondrial DNA
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
OCP	ongoing clinical pregnancy
PCR	polymerase chain reaction
PGS	preimplantation genetic screening
PPV	positive predictive value
QF-PCR	quantitative fluorescent PCR
VT	viability test

1. Introduction

Ovarian stimulation and in vitro fertilisation of oocytes with spermatozoa is widely used to treat couples with infertility or genetic disorders in order to assist with the conception of a child. Embryo selection techniques offer the potential to optimise the efficiency of the process. Embryo selection using genetic testing has primarily been used to detect chromosome aneuploidy (Preimplantation Genetic Screening, PGS), which is a common known cause of embryo failure [1,2]. Promising techniques continue to emerge which can detect aneuploidy for every chromosome, and potentially evaluate the viability of embryos with a normal chromosome complement [3-6]. Genetic testing offers the potential to transfer one embryo at a time in the fewest possible number of transfer procedures to optimise a woman's chance of achieving a healthy singleton live birth event, substantially reducing the risk of clinical complication associated with multiple pregnancy, and miscarriage due to chromosome aneuploidy.

There have been many advances in the technology used for genetic testing and assisted conception, and in particular reliable blastocyst culture and effective cryopreservation enable the sampling of multiple cells from an embryo with sufficient time to perform advanced genetic tests. Advances in cryopreservation techniques mean that it has now become possible to carry out serial transfer of all available embryos one at a time without genetic testing; this has the advantage of avoiding false abnormal results from genetic testing and therefore optimising the potential for of a live birth from a stimulated cycle [7]. In addition, there is evidence accumulating that the perinatal

outcome of IVF babies may be improved following cryopreservation of all embryos prior to transfer in cycles optimised for implantation rather than ovarian stimulation [8-10]. However, the disadvantage of serial single embryo transfer without genetic testing is that it may take longer to achieve success and with a substantial risk of miscarriage for the woman.

Much has been published concerning the advantages and disadvantages of sampling embryos at different stages, the different genetic testing techniques, which patient groups might benefit from testing embryos, which outcome measures are the most appropriate and what constitutes a well-designed clinical trial, and the current status of the clinical evidence available [11-18]. Whilst it is recognised that much of the published data does not meet the highest level of medical evidence, many eminent scientists and clinicians in the field have expressed the opinion in a recent statement that PGS should no longer be considered an experimental procedure and should be discussed with all patients considering assisted conception [19].

One specific limitation of the published randomised controlled trials was that they did not include the outcome of cryopreserved embryos, which could contribute to the cumulative pregnancy rate [16], and the absence of cost-effectiveness studies has also been highlighted [18]. The aim of the theoretical study presented here is to explore the cost-effectiveness of genetic testing, and its potential to improve a woman's chance of success for a full cycle of in vitro fertilisation.

2. Materials and Methods

2.1. Study model

A decision model was constructed for the transfer of all suitable embryos (blastocysts say), one at a time, from a stimulated cycle where up to ten transferable embryos were available, until a first live birth was achieved or there were no more embryos (a full cycle). Two transfer strategies were investigated: (i) freeze-all prior to warmed serial replacement, and (ii) one fresh transfer with subsequent serial warmed embryo replacement (Figure 1). A flexible Microsoft Excel version of the model is available as supplementary material, which includes a worked example of the solution for three embryos.

2.2. Baseline probabilities and populations

Baseline reproductive outcome and diagnostic accuracy data (Table 1, Supplementary Appendix 1) were obtained from two published prospective non-selection studies, where embryo transfer occurred without using the results from the genetic test for women undergoing IVF with an average age of 34 years (range 28 to 42 years). Two genetic tests were envisaged: (a) an aneuploidy test (AT) for every chromosome [20], and (b) a viability test (VT) for embryos with a normal chromosome complement detected following an aneuploidy test [5]. A 94% warming survival rate following blastocyst biopsy was assumed from a published study [21] and the rate was varied in a sensitivity analysis. The primary outcome measure was the live birth rate per full cycle, secondary measures were the live birth rate following a first transfer attempt, the total number of transfer attempts, and the clinical miscarriage rate per full cycle.

A final analysis, specifically for good prognosis patients (maternal age less than 35 years, normal karyotype, no prior miscarriages), was done using data obtained from a published prospective randomised control trial [22]. The primary reproductive outcome was ongoing clinical pregnancy (Table 1).

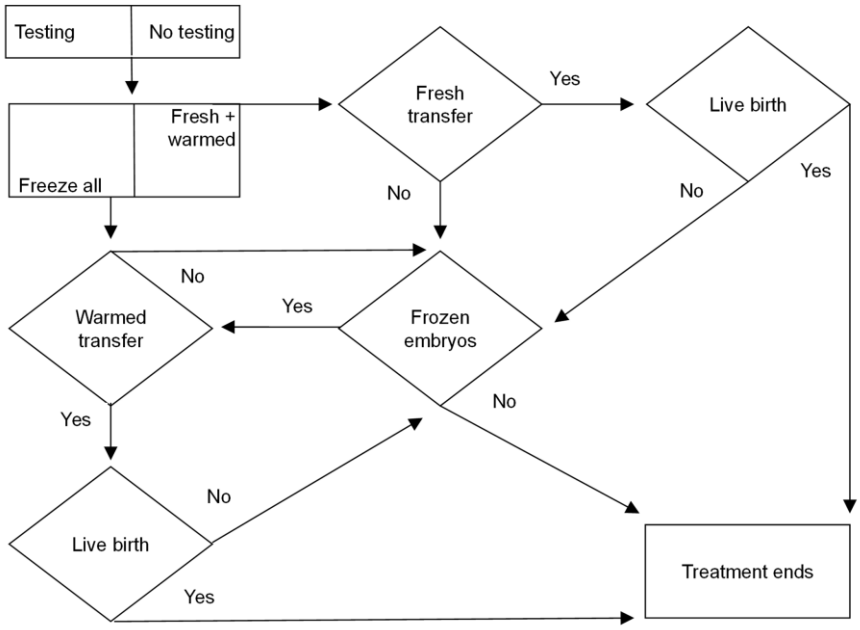

Figure 1. Model flow chart.

Footnote: The number of embryos available for transfer and cryopreservation is affected by the diagnostic accuracy of the test. The number of embryo transfer attempts is affected by the warming survival rate. The number of miscarriages and live births where a transfer occurs is determined by the outcome rates (see Table 1).

Table 1. Putative assisted conception populations and baseline probabilities.

Female partner aged 18 to 42 years	Genetic test positive predictive value (PPV)[§]	Live birth rate per transfer	Miscarriage rate per clinical pregnancy
No test	-	0.25431 (25.4%)	0.08475 (8.5%)
Aneuploidy testing (AT)	0.9596 (96%)	0.41353 (41.4%	0.05085 (5.1%)
Aneuploidy testing (optimised)	1 (100%)	0.43066 (43.1%)	0.05085 (5.1%)
AT plus viability testing (VT)	0.97222 (97.2%)	0.625 (62.5%)	0 (0%)
AT plus VT (optimised)	1 (100%)	0.6413 (64.1%)	0 (0%)
Good prognosis, female partner aged <35 years	Genetic test positive predictive value (PPV)[§]	Ongoing clinical pregnancy rate per transfer	Miscarriage rate per clinical pregnancy
No test	-	0.41667 (41.7%)	0.09091 (9.1%)
AT	0.91945 (92%)	0.69102 (69.1%)	0.02564 (2.6%)
AT (optimised)	1 (100%)	0.71008 (71%)	0.02564 (2.6%)
AT plus VT	0.93389 (93.3%)	0.84092 (84.1%)	0 (0%)
AT plus VT (optimised)	1 (100%)	0.8527 (85.3%)	0 (0%)

[§] Test perspective, the proportion of abnormal test results that are correct (no live birth/ongoing clinical pregnancy event). Data and calculations are provided in Supplementary Appendix 1.

2.3. Costs

Baseline costs were obtained from websites and publications and adjusted to 2015 UK pounds sterling where necessary (Table 2). It was assumed:

- Genetic testing required eggs to be fertilised using ICSI in order to minimise the risk of DNA contamination from supernumerary sperm associated with IVF; however, the analysis also accommodates testing technologies that do not require ICSI.
- A pregnancy following genetic testing of embryos did not have prenatal diagnosis.
- The proportion of pregnancies resulting from embryos without genetic testing that had prenatal diagnosis was estimated to be 5%, based on screening using the integrated test for women aged 35 to 39 years [23].
- All clinical miscarriages involved a dilation and curettage procedure.
- Costs associated with managing a multiple pregnancy, preterm and neonatal complications would not have a material effect on the incremental cost-effectiveness ratio because only one embryo was transferred at a time with and without testing.

The calculation of the total cost for a full cycle for any given number of embryos was based on:

[Total number of women × (IVF/ICSI/PGS cycle cost + stimulation drugs)] +
[Total number of warmed embryo transfers × (FET cycle cost + FET drugs)] +
[Number of clinical miscarriages × proportion with D&C × (D&C cost + productivity loss)] +
[(Number of live births + number of clinical miscarriages) × proportion with PND × (PND cost + productivity loss)]

Table 2. Baseline costs.

Procedure	Median cost (£)	Range (£)
In vitro fertilisation (IVF) [24][§]	3475	1600 to 7221
Stimulation drugs [25]	900	600 to 1200
Frozen embryo transfer (FET) [24][§§]	1150	1000 to 1750
FET drugs [25]	150	-
Microarray aneuploidy screening (PGS) [24]	2975	2950 to 3000
PCR mtDNA viability screening [26]	200	-
Intracytoplasmic sperm injection (ICSI) [25]	1000	-
Dilation and curettage (D&C) [24]	2143	1046 to 2988
CVS/QF-PCR or amniocentesis/full karyotyping [27]	500	-
Loss of maternal productivity due to clinical miscarriage (2 days) [28][§§§]	247	-
Loss of maternal productivity due to prenatal diagnosis (0.5 day) [28][§§§]	62	-

[§] Assumed to exclude the cost for medication, and to include medical and nurse appointments, scans, egg collection, blastocyst culture, embryo transfer, and a pregnancy scan or a follow up consultation with the doctor.

[§§] Assumed to exclude the cost for medication, and to include consultations, scans and follow-up.

[§§§] UK median full-time gross annual earnings and assuming 220 working days per year.

Cost was assessed from the perspective of society using the incremental cost-effectiveness ratio (ICER), the difference in cost for one additional live birth event or one clinical miscarriage avoided.

The National Institute for Health and Care Excellence (NICE) guideline of £20,000 to £30,000 was used as the cost-effectiveness threshold for live births [29]. A position value of ten times the cost of a dilation and curettage (D&C) procedure was used for clinical miscarriage. Assisted conception and genetic testing baseline costs were varied in univariate sensitivity analyses, and the precision of the ICER was assessed using Monte Carlo simulation.

2.4. Statistical analysis

Odds and risk ratios were calculated to compare reproductive outcomes [30]; the 95% confidence interval was used to indicate precision, and *p*-values of less than 0.05 were considered to be statistically significant. Monte Carlo simulations for the ICER used 10,000 iterations and assumed that the differences in outcome and cost were normally distributed; calculations were made using Microsoft Excel function NORM.INV(RAND(),difference,standard_deviation).

2.5. Ethical approval

It was not necessary to obtain ethical approval or patient consent for this theoretical study.

3. Results

3.1. Transfer strategy (i) freeze-all prior to warmed serial transfer

In the first instance it was assumed that every embryo was potentially available for transfer (100% warming survival) and that none was excluded incorrectly due to the genetic test (100% PPV for AT or AT + VT). Per 100,000 couples the live birth rate per full cycle was 25.4% where one embryo was available and 94.7% for ten embryos, and was the same with or without testing; however, this was achieved with fewer transfer attempts overall following testing (Table 3, scenario A).

AT, two embryos: 103,086 vs 174,569 (difference −40.9%, 95% CI −40.7% to −41.2%)
AT, ten embryos: 219,861 vs 372,317 (difference −40.9%, 95% CI −40.8% to −41.1%)
AT + VT, two embryos: 69,225 (difference −60.3%, 95% CI −60.1% to −60.6%)
AT + VT, ten embryos: 147,642 (difference −60.3%, 95% CI −60.2% to −60.5%)

In sensitivity analyses, reducing the warming survival rate decreased the live birth rate per full cycle to the same degree with or without testing (Table 3, scenario B); however, reducing the positive predictive value of the test favoured not testing (Table 3, scenarios C). Testing was effective to avoid clinical miscarriage (Table 3, all scenarios).

For a live birth event following the first attempt (when two or more embryos were available), genetic testing was more effective than not testing (Table 3, all scenarios).

(a) Aneuploidy testing alone (Table 3, scenario A): 1.6 times (OR 1.638, 95% CI 1.607 to 1.670, $p < 0.001$) for two embryos, and 2.2 times (OR 2.217, 95% CI 2.176 to 2.260, $p < 0.001$) for ten embryos;
(b) Aneuploidy plus viability testing (Table 3, scenario A): 2.0 times (OR 2.019, 95% CI 1.981 to 2.058, $p < 0.001$) for two embryos, and 5.2 times (OR 5.150, 95% CI 5.052 to 5.250, $p < 0.001$) for ten embryos.

Table 3. Freeze-all serial embryo transfer strategy outcomes.

100,000 couples	No genetic testing				Genetic testing for aneuploidy (AT)				Genetic testing for aneuploidy and viability (AT + VT)			
No. of embryos	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt
Scenario A: 100% embryo warming survival, 100% positive predictive value (PPV) for AT and VT												
1	25,431	2355	100,000	25,431	25,431	1362	59,052	25,431	25,431	0	39,655	25,431
2	44,395	4111	174,569	25,431	44,395	2378	103,086	35,844	44,395	0	69,225	40,777
3	58,536	5420	230,174	25,431	58,536	3136	135,923	40,109	58,536	0	91,276	50,038
4	69,080	6397	271,639	25,431	69,080	3701	160,408	41,855	69,080	0	107,718	55,626
5	76,944	7125	302,558	25,431	76,944	4122	178,667	42,570	76,944	0	119,979	58,999
6	82,807	7668	325,615	25,431	82,807	4436	192,282	42,862	82,807	0	129,123	61,034
7	87,179	8073	342,808	25,431	87,179	4671	202,435	42,982	87,179	0	135,940	62,262
8	90,440	8375	355,628	25,431	90,440	4845	210,006	43,031	90,440	0	141,024	63,003
9	92,871	8600	365,188	25,431	92,871	4975	215,651	43,051	92,871	0	144,815	63,450
10	94,684	8768	372,317	25,431	94,684	5073	219,861	43,060	94,684	0	147,642	63,720
Scenario B: 94% embryo warming survival, 100% PPV for AT and VT												
1	23,905	2214	94,000	23,905	23,905	1281	55,509	23,905	23,905	0	37,276	23,905
2	42,096	3898	165,529	25,339	42,096	2255	97,748	34,541	42,096	0	65,641	38,899
3	55,938	5180	219,959	25,426	55,938	2997	129,890	39,273	55,938	0	87,225	48,305
4	66,471	6155	261,378	25,431	66,471	3561	154,349	41,378	66,471	0	103,649	54,204
5	74,486	6897	292,895	25,431	74,486	3991	172,960	42,315	74,486	0	116,147	57,904
6	80,585	7462	316,878	25,431	80,585	4317	187,123	42,731	80,585	0	125,658	60,225
7	85,226	7892	335,128	25,431	85,226	4566	197,900	42,917	85,226	0	132,895	61,681
8	88,758	8219	349,015	25,431	88,758	4755	206,100	42,999	88,758	0	138,402	62,594
9	91,445	8468	359,583	25,431	91,445	4899	212,341	43,036	91,445	0	142,592	63,167
10	93,490	8657	367,624	25,431	93,490	5009	217,089	43,052	93,490	0	145,781	63,526

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Table 3. Freeze-all serial embryo transfer strategy outcomes—continued.

100,000 couples	No genetic testing				Genetic testing for aneuploidy (AT)				Genetic testing for aneuploidy and viability (AT + VT)			
No. of embryos	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt	Live birth events (LB)	Clinical miscarriages	Embryo transfers	LB first attempt
Scenario C: 94% embryo warming survival, 96% PPV for AT and 100% for VT												
1	23,905	2214	94,000	23,905	22,285	1194	53,888	22,285	22,285	0	35,655	22,285
2	42,096	3898	165,529	25,339	39,603	2122	95,768	32,560	39,603	0	63,365	36,624
3	55,938	5180	219,959	25,426	53,062	2843	128,315	37,299	53,062	0	84,899	45,850
4	66,471	6155	261,378	25,431	63,522	3403	153,609	39,484	63,522	0	101,635	51,787
5	74,486	6897	292,895	25,431	71,651	3839	173,266	40,491	71,651	0	114,641	55,607
6	80,585	7462	316,878	25,431	77,969	4177	188,543	40,956	77,969	0	124,749	58,065
7	85,226	7892	335,128	25,431	82,878	4440	200,415	41,170	82,878	0	132,604	59,646
8	88,758	8219	349,015	25,431	86,694	4645	209,642	41,269	86,694	0	138,709	60,664
9	91,445	8468	359,583	25,431	89,659	4803	216,812	41,314	89,659	0	143,454	61,319
10	93,490	8657	367,624	25,431	91,963	4927	222,385	41,335	91,963	0	147,141	61,740

3.2. Transfer strategy (ii) fresh plus warmed serial embryo transfer

In the first instance it was assumed that every embryo was potentially available for transfer (100% warming survival) and that none was excluded incorrectly due to the genetic test (100% PPV); the live birth rate per full cycle, with and without testing, was the same as for the freeze-all strategy (Table 3, scenario A). However, in a sensitivity analysis, testing was favoured when the embryo warming survival rate was reduced and more than one transferable embryo was available. Figure 2A shows the effect when warming survival was 94% and the positive predictive value was 100% for aneuploidy testing (AT) and aneuploidy plus viability testing (AT + VT). The greater effect was for AT + VT; per 100,000 couples, testing was effective for live birth when more than one embryo was available and with fewer transfer attempts (Supplementary Appendix 2, Table S2a):

Two embryos: CLBR 44.2% vs 43.3% (difference 2.1%, 95% CI 1.1% to 3.2%, $p < 0.001$) with 59.5% (95% CI 59.2% to 59.8%) fewer transfer attempts (68,887 vs 170,095)

Ten embryos: CLBR 94.1% vs 93.6% (difference 0.5%, 95% CI 0.2% to 0.7%, $p < 0.001$) with 60.2% (95% CI 60.0% to 60.3%) fewer transfer attempts (146,668 vs 368,137)

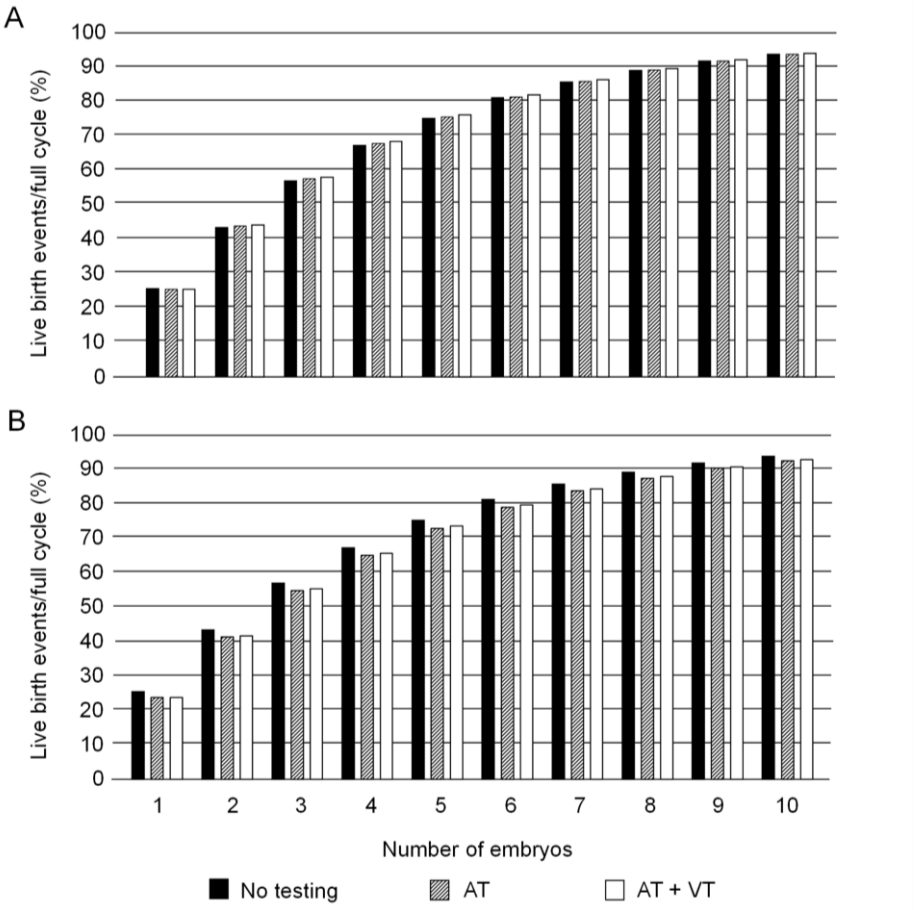

Figure 2. Live birth rate per full cycle using a fresh plus warmed transfer strategy with 94% embryo warming survival. A—100% positive predictive value (PPV) for aneuploidy testing (AT) and viability testing (VT); B—96% PPV for AT, and 100% PPV for VT.

Testing was less effective than not testing when the positive predictive value for AT was reduced to the 96% estimated from the study of Scott and colleagues [20] (Figure 2B); however, genetic testing was favoured for a first attempt, when two or more embryos were available (Figure 3A), and was effective for a full cycle to avoid clinical miscarriage (Figure 3B).

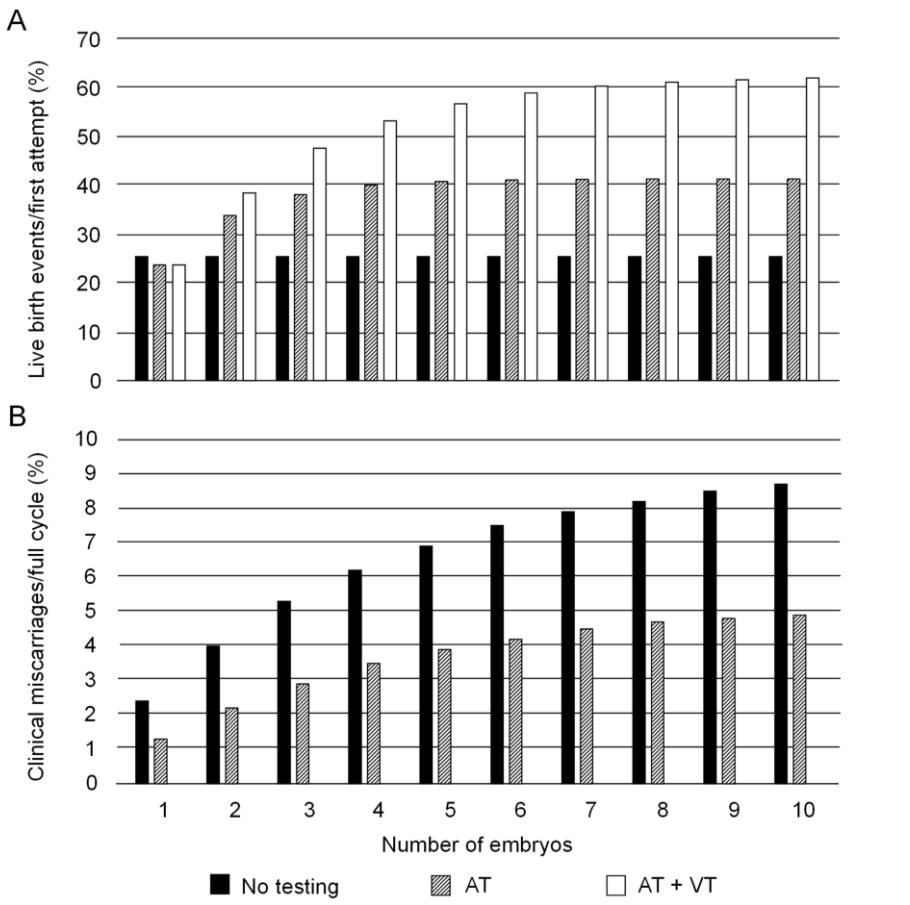

Figure 3. Fresh plus warmed transfer strategy with 94% embryo warming survival, and 96% positive predictive value for aneuploidy testing and 100% for viability testing. A—Live birth rate for a first transfer attempt; B—Clinical miscarriage rate for a full cycle.

The results for the analysis based on the clinical trial of Yang and colleagues are shown in Table 4 [22]. The positive predictive value of the aneuploidy test was estimated to be 92% and was assumed to be 100% for the viability test (Table 1). For a fresh plus frozen transfer strategy with 94% embryo warming survival, genetic testing was less effective for ongoing clinical pregnancy over a full cycle. For aneuploidy testing alone, the CLBR was 38.0% vs 41.7% (difference −8.7%, 95% CI −8.4% to −9.0%) for one embryo, 98.94% vs 99.33% (difference −0.39%, 95% CI −0.36% to −0.43%) for ten embryos.

Table 4. Women with a good prognosis. Ongoing clinical pregnancy rate for a full cycle with a fresh plus warmed embryo transfer strategy and assuming 94% embryo warming survival, and 92% and 100% positive predictive value respectively for the aneuploidy and viability genetic tests.

100,000 couples	No genetic testing				Genetic testing for aneuploidy				Genetic testing for aneuploidy and viability			
No. of embryos	Ongoing clinical pregnancies (OCP)	Clinical miscarriages	Embryo transfers	OCP first attempt	Ongoing clinical pregnancies (OCP)	Clinical miscarriages	Embryo transfers	OCP first attempt	Ongoing clinical pregnancies (OCP)	Clinical miscarriages	Embryo transfers	OCP first attempt
1	41,667	4,167	100,000	41,667	38,047	1,001	55,059	38,047	38,047	0	45,244	38,047
2	64,514	6,451	154,833	41,667	61,230	1,611	88,608	55,146	61,454	0	73,079	58,880
3	78,413	7,841	188,190	41,667	75,557	1,988	109,341	62,830	75,924	0	90,286	70,287
4	86,868	8,687	208,481	41,667	84,506	2,224	122,291	66,283	84,909	0	100,971	76,534
5	92,011	9,201	220,826	41,667	90,140	2,372	130,445	67,835	90,512	0	107,633	79,954
6	95,140	9,514	228,335	41,667	93,708	2,466	135,608	68,533	94,017	0	111,802	81,826
7	97,044	9,704	232,903	41,667	95,977	2,526	138,892	68,846	96,219	0	114,419	82,852
8	98,202	9,820	235,682	41,667	97,424	2,564	140,986	68,987	97,605	0	116,068	83,413
9	98,906	9,891	237,372	41,667	98,349	2,588	142,324	69,051	98,480	0	117,108	83,721
10	99,334	9,934	238,401	41,667	98,941	2,604	143,181	69,079	99,034	0	117,767	83,889

However, when two or more embryos were available, compared to not testing, genetic testing was favoured for a first attempt, with fewer attempts overall.

(a) Aneuploidy testing alone: 1.7 times (OR 1.721, 95% CI 1.691 to 1.752, $p < 0.001$) and 88,608 vs 154,833 attempts (difference −42.7%, 95% CI −42.5% to −43.0%) for two embryos, and 3.1 times (OR 3.128, 95% CI 3.071 to 3.186, $p < 0.001$) and 143,181 vs 238,401 attempts (difference −39.9%, 95% CI −39.7% to −40.1%) for ten embryos;

(b) Aneuploidy plus viability testing: 2.0 times (OR 2.005, 95% CI 1.969 to 2.041, $p < 0.001$) and 73,079 attempts (difference −52.8%, 95% CI −52.6% to −53.1%) for two embryos, and 7.3 times (OR 7.29, 95% CI 7.138 to 7.445, $p < 0.001$) and 117,767 attempts (difference −50.6%, 95% CI −50.4% to −50.8%) for ten embryos.

3.3. Cost-effectiveness from the society perspective

Table 5 shows a summary of the analyses for the population where the maternal age range was 18 to 42 years, the data are provided as supplementary appendix 2. There were four scenarios where the number of live birth events was greater with testing (scenarios 1, 3, 5 and 7; fresh plus warmed embryo transfer and 100% PPV). The live birth ICER was less than £30,000 only for scenario 1 (ICSI with no testing vs ICSI with AT + VT [Supplementary Table S2b], or IVF with no testing vs IVF with AT + VT [Supplementary Table S2c]) and when nine (ICER = £25,790) or ten transferable embryos (ICER = £15,588) were available. A Monte Carlo simulation for nine embryos indicated that testing was more effective for live birth in 100% of trials; the ICER range was £22,365 to £30,572, and less than £30,000 in 99.94% of trials (Table 6).

The cost of aneuploidy testing was reduced by 50% for the effective scenarios (Table 6). For scenarios 1, 3 and 5, reducing the cost of the genetic test reduced the number of embryos required for the cost of an additional live birth to be less than £30k, and the cost for a miscarriage prevented to be less than £23.9k (ten times the dilation and curettage cost). The test cost reduction was not sufficient to bring scenario 7 within the range of the study. The fewest number of embryos required was for scenario 1 (three embryos), where ICSI was required for treatment (or the genetic test does not require ICSI and IVF can be used for both groups).

Genetic testing was likely to be less effective than not testing for an ongoing clinical pregnancy for younger women (less than 35 years) with a good prognosis. There were likely to be fewer miscarriages following testing; however, using the base costs, the cost for each miscarriage avoided might be considered to be expensive (Supplementary Table S6b):

(a) Aneuploidy testing alone: the ICER ranged between £91,184 (38x D&C) for one embryo and £20,896 (9x D&C) for ten embryos

(b) Aneuploidy plus viability testing: the ICER ranged between £73,499 (31x D&C) for one embryo and £13,508 (6x D&C) for ten embryos.

Table 5. Summary of cost-effectiveness analyses.

Scenario [suppl. Table]	Transfer strategy	Warming survival (%)	No genetic testing	ICSI + genetic testing	Genetic test PPV (%)	Live birth events: testing > not testing	Live birth ICER <£30K	Miscarriage ICER <10x D&C
1 [S2b]§	Fresh + warmed	94	ICSI	AT + VT	100	Yes	>8 embryos	>3 embryos
2 [S4b]§	Fresh + warmed	94	ICSI	AT + VT	96 & 100	No	-	>3 embryos
3 [S2b]§	Fresh + warmed	94	ICSI	AT	100	Yes	-	-
4 [S4b]§	Fresh + warmed	94	ICSI	AT	96	No	-	-
5 [S2d]	Fresh + warmed	94	IVF	AT + VT	100	Yes	-	>5 embryos
6 [S4c]	Fresh + warmed	94	IVF	AT + VT	96 & 100	No	-	>5 embryos
7 [S2d]	Fresh + warmed	94	IVF	AT	100	Yes	-	-
8 [S4c]	Fresh + warmed	94	IVF	AT	96	No	-	-
9 [S3b]§	Freeze-all	94	ICSI	AT + VT	100	No	-	>2 embryos
10 [S5b]§	Freeze-all	94	ICSI	AT + VT	96 & 100	No	-	>2 embryos
11 [S3b]§	Freeze-all	94	ICSI	AT	100	No	-	>5 embryos
12 [S5b]§	Freeze-all	94	ICSI	AT	96	No	-	>5 embryos
13 [S3c]	Freeze-all	94	IVF	AT + VT	100	No	-	>3 embryos
14 [S5c]	Freeze-all	94	IVF	AT + VT	96 & 100	No	-	>3 embryos
15 [S3c]	Freeze-all	94	IVF	AT	100	No	-	-
16 [S5c]	Freeze-all	94	IVF	AT	96	No	-	-

§ For ICSI without testing vs ICSI with testing comparisons, the ICER is the same for IVF without testing vs IVF with testing (ICSI not a requirement for genetic testing)

Table 6. Cost-effectiveness analysis testing as few as two embryos for scenarios effective for a live birth event.

Scenario (fresh + warmed, 94%) [Suppl. Table]	Genetic testing cost (£) (PPV 100% for AT and VT)	Live birth ICER <£30k	Live birth ICER (£)	Monte Carlo simulation, 10,000 trials		Miscarriage ICER <10x D&C
				ICER range (£)	ICER <£30k (trials %)	
Base genetic testing costs						
1 (ICSI) [S2b]	3175 : 2975 (AT) + 200 (VT)	9+ embryos	25,790	22,365 to 30,572	99.94	4+ embryos
3 (ICSI) [S2b]	2975 : 2975 (AT)	-	-	-	-	-
5 (IVF) [S2d]	3175 : 2975 (AT) + 200 (VT)	-	-	-	-	6+ embryos
7 (IVF) [S2d]	2975 : 2975 (AT)	-	-	-	-	-
Aneuploidy test base cost reduced by 50%						
1 (ICSI) [S2e]	1688 : 1488 (AT) + 200 (VT)	3+ embryos	8210	7437 to 9285	100	2+ embryos
3 (ICSI) [S2e]	1488 (AT)	4+ embryos	8570	7476 to 10,128	100	3+ embryos
5 (IVF) [S2f]	1688 : 1488 (AT) + 200 (VT)	5+ embryos	26,461	24,031 to 30,087	99.99	3+ embryos
7 (IVF) [S2f]	1488 (AT)	-	-	-	-	6+ embryos

4. Discussion

Genetic testing was envisaged to encompass the latest and emerging techniques for chromosome copy number enumeration and for assessing the reproductive competence of embryos with a normal chromosome complement. Microarray techniques are widely used to test preimplantation embryos for chromosome aneuploidy, which is usually not compatible with life, but a substantial proportion of embryos with a normal test result fail to make a baby [20]. Different promising techniques designed to look for genetic markers of embryo viability (VT) are emerging, which may improve the ability of a test to select the best embryo for transfer [3,5]. This study assessed the likely potential of only testing for chromosome aneuploidy (AT) using the best possible technique, and also imagined the hypothetical possibility of a test which could select viable embryos (AT + VT) without excluding any due to an incorrect test result.

When only one embryo is available, testing cannot be more effective for live birth because there is no potential for selection, whether or not the embryo is cryopreserved before transfer. When more than one embryo is available, the analysis presented here supports the argument that using a freeze-all strategy no embryo selection technique can improve on the serial transfer of every warmed embryo from a stimulation to achieve a live birth, and demonstrates that caution should be exercised when drawing a conclusion about the effectiveness of PGS if a trial does not include the outcome of cryopreserved embryos [16]. However, substantially fewer transfer attempts following testing are likely to be needed, with the potential to minimise the treatment time.

A fresh plus warmed transfer strategy has the potential to be more effective for live birth when more than one embryo is available because selection increases the probability that a viable embryo is replaced in the fresh transfer and evades the attrition associated with embryo warming following cryopreservation. The study presented here indicates that in the context of a full cycle with efficient cryopreservation, the increase in the live birth rate using genetic testing is likely to be marginal, and was estimated to be up to 2.1% assuming 94% warming survival and a test with no false abnormal results; however, this was negated when the predictive value of an abnormal test result for the aneuploidy test is 96% rather than 100%. A limitation of the model is that it assumes that every embryo suitable for transfer within each group has the same potential to achieve a live birth, and is the same for fresh or warmed replacement.

The model explored the effect on outcome and the incremental cost-effectiveness ratio of different numbers of embryos available for transfer. Using base costs, none of the scenarios for aneuploidy testing alone had an ICER <£30k for live birth, and only one scenario testing for aneuploidy plus viability (100% PPV, fresh plus frozen transfer, both groups using ICSI or both groups using IVF if ICSI is not required for the test), when nine or ten embryos were available for transfer. The costs associated with genetic testing and ICSI (which might only be required to facilitate genetic testing) had a material effect on the ICER for live birth and clinical miscarriage. Testing is more likely to be cost-effective if ICSI is necessary anyway (or not a requirement for genetic testing), and if a substantial reduction in the cost of the genetic test is possible. However, caution is advised since it is yet to be demonstrated that genetic testing of embryos can improve the chance of a live birth for a full cycle or eliminate the risk of miscarriage.

Serial single embryo transfer following testing is likely to be more effective for clinical miscarriage, but the analysis presented here indicates that it is likely to be expensive and it is debatable whether society would consider this to be cost-effective. The author is aware of one

published study to date, which compared PGS for every chromosome with expectant management in patients with recurrent pregnancy loss, and concluded that PGS was not a cost-effective strategy for increasing live birth, and a very costly way to reduce miscarriage [31].

Outcome measures which incorporate fresh as well as warmed cryopreserved embryo transfer (cumulative rate) rather than success rates based on only fresh transfer is recognised to be more appropriate for decision making regarding the efficacy of treatment and cost [32]. The study presented here is analogous to that recommended for short term reporting (outcome episodes per woman for one egg collection in a two year period) [32], with the exception that only women with embryos are included since genetic testing cannot occur otherwise.

The analysis of the Yang and colleagues trial [22] for young women with good prognosis shows that we should expect that testing will be highly effective for an ongoing clinical pregnancy following a first attempt, with fewer attempts required overall (and potential for less time in treatment). However, had the study included serial transfer of available warmed cryopreserved embryos in a full cycle, it is likely that testing embryos for aneuploidy would have been less effective for ongoing clinical pregnancy with the 92% test PPV estimated for the study. The predictive value of an aneuploid test result is sensitive to the prevalence of aneuploidy and therefore the PPV may be expected to be less for younger women [33,34]. A less than 1% difference in the cumulative ongoing pregnancy rate when larger numbers of embryos are available for younger women might be considered to be marginal, but the incremental cost for each miscarriage avoided may be considered to be expensive at greater than nine times the cost of dilation and curettage.

The current study was limited to one full cycle of in vitro fertilisation and assumed that every suitable embryo available was transferred until a first live birth event was achieved (there was no intra-cycle dropout and treatment was completed). A woman may require more than one stimulation cycle to achieve a live birth event and it is expected that some women will dropout within and between cycles [35]. Important reasons for prematurely continuing treatment appear to include not becoming pregnant and cost, and some women chose not to continue following a miscarriage [36]. Further work is required to analyse the effect of PGS on pregnancy outcome and cost-effectiveness where women have the opportunity to have more than one stimulated cycle.

5. Conclusion

PGS should be expected to be more effective for live birth following a first transfer attempt and to require fewer transfer attempts overall. However, using a freeze-all transfer strategy, genetic testing is unlikely improve a couple's chance of a live birth event taking into account every embryo available for transfer from a stimulation. Compared to not testing, it is possible for PGS to be more effective using a fresh plus frozen transfer strategy when more than one embryo is available, but the increase in the chance of a live birth for a full cycle is likely to be marginal and to be negated when the positive predictive value of the test is suboptimum. PGS is more likely to be cost-effective for live birth when ICSI is required anyway, and if the testing can be made substantially less expensive. PGS is expected to be effective for clinical miscarriage for both strategies, but the cost of a miscarriage avoided may be perceived by society to be expensive. There is a need for clinical trials using outcome measures which incorporate fresh as well as warmed cryopreserved embryo transfer (cumulative rate) for decision making regarding the efficacy of treatment and cost, and to help better inform individual patients considering assisted conception.

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Conflict of interest

None declared.

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