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Investigating the effect of ethnicity on IVF outcome

Rima K Dhillon [a,*], Paul P Smith [a], Rosamund Malhas [a], Hoda M Harb [a], Ioannis D Gallos [a], Ken Dowell [b], Simon Fishel [b], Jon J Deeks [c], Aravinthan Coomarasamy [a]

[a] *Academic Department, Birmingham Women's Hospital Foundation Trust, Metchley Park Road, Edgbaston, Birmingham, B15 2TG, UK;* [b] *CARE (Centres for Assisted Reproduction) John Webster House, 6 Lawrence Drive, Nottingham Business Park, Nottingham, NG8 6PZ, UK;* [c] *School of Health and Population Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK*

* Corresponding author. *E-mail address:* rima.dhillon@doctors.org.uk (RK Dhillon).

Dr Rima Dhillon is a junior Obstetrics and Gynaecology trainee. She is currently the Clinical Research Fellow for the national multi-centre TABLET Trial, and is based at the Birmingham Womens Hospital. Rima is also in her final year of her PhD titled "Risk stratification for patients undergoing in-vitro fertilisation" at the University of Birmingham, and has several publications to her name. Her passion lies within the field of reproductive medicine and she hopes to sub-specialize in this area as her career progresses.

Abstract Success rates for IVF among women from different ethnic groups have been inconclusive. In this study, the relationship between ethnicity and IVF outcome was investigated. Results of a cohort study analysing 13,473 first cycles were compared with the results of meta-analysed data from 16 published studies. Adjustment was made for age, body-mass index, cause of infertility, duration of infertility, previous live birth, previous spontaneous abortion and number of embryos transferred. Black and South Asian women were found to have lower live birth rates compared with White women: Black versus White (OR 0.42 [0.25 to 0.70]; $P = 0.001$); South Asian versus White (OR 0.80 [0.65t o 0.99]; $P = 0.04$). Black women had significantly lower clinical pregnancy rates compared with White women (OR 0.41 [0.25 to 9 0.67]; $P < 0.001$). The meta-analysed results also showed that Black and South Asian women had statistically significant reduced odds of live birth (OR 0.62 [0.55 to 0.71); $P < 0.001$ and OR 0.66 [0.52 to 0.85); $P = 0.001$, respectively). Black and South Asian women seem to have the poorest outcome, which is not explained by the commonly known confounders. Future research needs to investigate the possible explanations for this difference and improve IVF outcome for all women.

KEYWORDS: assisted conception, ethnicity, in-vitro fertilisation, race

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Introduction

Ethnicity is a commonly investigated prognostic factor in medicine. Few studies, however, have been able to clearly explore the association between ethnicity and IVF outcomes. Ethnic minorities account for 13% of the UK population (Census 2011, n.d.). It is important for couples undergoing assisted conception to be counselled appropriately and according to their individual backgrounds.

The existing literature on ethnicity and IVF outcomes consists largely of US studies that focus on Hispanic and African American groups. Although large studies have used the Society of American Reproductive Technologies (SART) database (Seifer et al., 2008, 2010), such studies have not been able to adjust their findings to key confounders; furthermore, the ethnic mix of the US population is widely different from that of the UK. Therefore, the findings of these studies may not be transferrable, thus prompting the need for a large UK study. In the UK, three studies have explored the association between ethnicity and IVF outcome (Jayaprakasan et al., 2014; Lashen et al., 1999; Mahmud et al., 1995). Two of these were conducted over 10 years ago (Lashen et al., 1999; Mahmud et al., 1995), so there is a question about their applicability to today's population given the rapid advances in IVF over the years. The most recent publication (Jayaprakasan et al., 2014) was limited by its sample size ($n = 1517$) and did not differentiate between ethnic groups.

The aim of this study was to investigate the relationship between ethnicity and IVF outcome, while adjusting for known confounders. Evidence is also presented on the relationship between ethnicity and assisted conception outcome incorporating a meta-analysis of the existing published data.

Materials and methods

Study design

This observational cohort study included all women undergoing their first non-donor cycle of IVF or intracytoplasmic sperm injection (ICSI) at any Centres for Assisted Reproduction (CARE) clinic in the UK and Ireland between 2008 and 2012. CARE is one of the UK's largest independent provider of fertility services and in which both National Health Service (NHS) and non-NHS patients are treated. Permission for use of the database was granted by the CARE International Review Board, following review of the study protocol. The dataset was anonymized according to the Information Commissioner's Office guide on non-identifiable data. Furthermore, the CARE data protection certificate allows for their data to be used for survey and research purposes.

Data were analysed from five main fertility clinics within the CARE consortium; Nottingham, Manchester, Northampton, Sheffield and Dublinm and a further seven nationally spread satellite centres; Bolton, Boston, Derby, Leicester, Mansfield, Milton Keynes and Peterborough. Both fresh and frozen assisted conception cycle data were included.

All women undergoing treatment at CARE are required to complete their demographic profile. The ethnicity definitions were in line with that of the Human Fertilisation and Embryology coding. A total of 17 individual ethnic groups were divided into seven main categories; White (White British, White Irish, any other White), South Asian (Indian, Pakistani, Bangladeshi, any other Asian background), Black (Black Caribbean, Black African, other Black), Chinese, mixed (White and Black Caribbean, White and Black African, White and Asian, any other mixed), any other and not stated.

Statistical analysis

Baseline patient characteristics, cycle characteristics and outcome data were described giving frequencies with percentages, or means with standard deviations, as appropriate. To estimate the contribution of ethnicity to live birth rate (defined as the birth of one of more living infants) and clinical pregnancy (defined as the presence of a gestational sac on ultrasound), univariate and multiple logistic regression analyses were conducted to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) along with *P*-values. $P < 0.05$ was considered to be statistically significant. Covariates were pre-selected when they had a known effect on IVF outcome, based on clinical knowledge and experience. The covariates selected for the multivariate model were age, body mass index, duration and cause of infertility, previous live birth, previous spontaneous abortion and number of embryos transferred. Ideally a measure of ovarian reserve (i.e. day 2 FSH, anti-Müllerian hormone or antral follicle count) would have been included; however, these variables were not well recorded in the database and so were removed from analysis. A sensitivity analysis of fresh and frozen cycles was carried out separately, breaking down the causes of infertility to specifically include fibroids. Data were analysed using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp., USA).

Results

A total of 13,473 cycles were reported between 2008 and 2012 at the CARE clinics in the UK. The ethnic groupings were as follows: White (10,062), Black (212), South Asian (1025), Chinese (83), mixed (476), other (148) and not stated (1467). An overall description of the results, including baseline patient characteristics, cycle characteristics and cycle outcomes are presented in **Tables 1–3**. The number of cycles that had data for each variable is specified within the tables. Black women had worse risk factors: they were on average older, had higher body mass indices, a greater number of previous spontaneous abortions, and a longer duration of infertility than White women. Asian women, however, were on average younger, had lower body mass indicies, greater rates of anovulation, lower rates of previous spontaneous abortion, but longer duration of infertility than White women. The group with unstated ethnic group had the highest rates of previous live births, lowest rates of previous spontaneous abortions but the longest duration of infertility.

Live birth rate was statistically significantly lower in Black women than White women (19.8% versus 34.7%; $P < 0.001$). Rates in South Asian women and White women were similar (33.3% versus 34.7%). The difference between Black and White women increased in magnitude and remained statistically

Table 1 Baseline characteristics across each ethnic group.[a]

	White (n = 10,062)	*Black (n = 212)*	P-*value*	*South Asian (n = 1025)*	P-*value*	*Chinese (n = 83)*	P-*value*	*Mixed (n = 476)*	P-*value*	*Other (n = 148)*	P-*value*	*Not stated (n = 1467)*	P-*value*
Age (in years)	(*n* = 10,062)	(*n* = 212)		(*n* = 1025)		(*n* = 83)		(*n* = 476)		(*n* = 148)		(*n* = 1467)	
<35, *n* (%)	5577 (55.4)	103 (48.6)	<0.05	731 (71.3)	<0.001	49 (59)	–	281 (59.0)	–	72 (48.6)	–	757 (51.6)	0.006
35.1–40, *n* (%)	3166 (31.5)	59 (27.8)	–	223 (21.8)	<0.001	25 (30.1)	–	133 (27.9)	–	61 (41.2)	0.01	459 (31.3)	–
40.1–45, *n* (%)	1112 (11.1)	39 (18.4)	<0.001	65 (6.3)	<0.001	9 (10.8)	–	53 (11.1)	–	15 (10.1)	–	188 (12.8)	<0.05
>45.1, *n* (%)	207 (2.1)	11 (5.2)	0.003	6 (0.6)	0.002	0	–	9 (1.9)	–	0	–	63 (4.3)	<0.001
Body mass index	(*n* = 5278)	(*n* = 116)		(*n* = 527)		(*n* = 45)		(*n* = 290)		(*n* = 86)		(*n* = 132)	
>18.5, *n* (%)	89 (1.7)	3 (2.6)	–	15 (2.8)	–	2 (4.4)	–	16 (5.5)	<0.001	0	–	0	–
18.6–25, *n* (%)	3100 (58.7)	35 (30.2)	<0.001	293 (55.6)	–	40 (88.9)	<0.001	160 (55.2)	–	58 (67.4)	–	85 (64.4)	–
25.1–30, *n* (%)	1625 (30.8)	48 (41.1)	0.02	178 (33.8)	–	2 (4.4)	0.002	81 (27.9)	–	25 (29.1)	–	32 (24.2)	–
30.1–35, *n* (%)	421 (8.0)	28 (24.1)	<0.001	33 (6.3)	–	0	–	30 (10.3)	–	3 (3.5)	–	12 (9.1)	–
>35.1, *n* (%)	43 (0.8)	2 (1.7)	–	8 (1.5)	–	1 (2.2)	–	3 (1.0)	–	0	–	3 (2.3)	–
Cause of infertility[b]													
Male factor, *n* (%)	5896 (58.6)	109 (51.4)	0.04	589 (57.5)	–	54 (65.1)	–	296 (62.2)	–	95 (64.2)	–	548 (37.4)	<0.001
Tubal factor, *n* (%)	1554 (15.4)	36 (17.0)	–	123 (12.0)	0.004	22 (26.5)	0.007	68 (14.3)	–	29 (19.6)	–	226 (15.4)	–
Anovulation, *n* (%)	1156 (11.5)	17 (8.0)		197 (19.2)	<0.001	7 (8.4)	–	58 (12.2)	–	17 (11.5)	–	200 (13.6)	0.02
Female other, *n* (%) (e.g. endometriosis), *n* (%)	3014 (30.0)	91 (42.9)	<0.001	230 (22.4)	<0.001	14 (16.9)	0.001	146 (30.7)	–	45 (30.4)	–	319 (21.7)	<0.001
Unexplained, *n* (%)	2948 (29.3)	60 (28.3)	–	343 (33.5)	0.006	23 (27.7)	–	130 (27.3)	–	34 (23.0)	–	437 (29.8)	–
Previous live birth, *n* (%)	1907 (19.0)	29 (13.7)	–	190 (18.5)	–	11 (13.3)	–	94 (19.7)	–	21 (14.2)	–	349 (23.8)	<0.001
Previous spontaneous abortion, *n* (%)	2047 (20.3)	61 (28.8)	0.003	163 (15.9)	<0.001	9 (10.8)	0.04	98 (20.6)	–	28 (18.9)	–	98 (6.7)	<0.001
Duration of infertility in years (Mean ± SD)	2.71 ± 2.1	3.5 ± 2.8	–	3.4 ± 2.7	<0.001	3.3 ± 2.8	–	2.6 ± 2.3	–	3.1 ± 2.5	–	4.4 ± 3.2	<0.001
Day 2 FSH	(*n* = 3214)	(*n* = 66)		(*n* = 343)		(*n* = 27)		(*n* = 215)		(*n* = 60)		(*n* = 64)	
(Mean ±SD)	8.13 ± 21.9	7.9 ± 3.8	–	7.3 ± 6.4	–	5.7 ± 2.1	<0.001	6.8 ± 2.5	0.002	6.6 ± 2.2	0.002	6.6 ± 1.9	<0.001
AMH level	(*n* = 1289)	(*n* = 13)		(*n* = 107)		(*n* = 8)		(*n* = 44)		(*n* = 15)		(*n* = 17)	
(Mean ±SD)	16.98 ± 18.2	20.5 ± 27.7	–	24.5 ± 33.5	0.02	25.0 ± 34.9	–	9.3 ± 11.3	<0.001	13.6 ± 9.9	–	26.7 ± 24.9	–
Antral follicle count	(*n* = 3987)	(*n* = 91)		(*n* = 359)		(*n* = 24)		(*n* = 199)		(*n* = 69)		(*n* = 42)	
(Mean ±SD)	20.7 ± 12.5	18.4 ± 13.5	–	20.3 ± 14.7	–	15.5 ± 7.4	0.002	19.3 ± 12.8	–	18.1 ± 13.5	–	27.6 ± 16.3	0.009

[a]Each ethnic group was compared with the reference group "White", only the statistically significant differences are reported.
[b]Not mutually exclusive.
AMH = anti-mullerian hormone.

Table 2 Cycle data.[a]

	White (n = 10,062)	*Black (n = 212)*	P-*value*	*South Asian (n = 1025)*	P-*value*	*Chinese (n = 83)*	P-*value*	*Mixed (n = 476)*	P-*value*	*Other (n = 148)*	P-*value*	*Not stated (n = 1467)*	P-*value*
Treatment													
IVF, *n* (%)	2704 (26.9)	60 (28.3)	–	252 (24.6)	–	26 (31.3)	–	96 (20.2)	0.001	38 (25.7)	–	359 (24.5)	<0.001
ICSI, *n* (%)	5010 (49.8)	106 (50)	–	556 (54.2)	0.01	30 (36.1)	0.01	270 (56.7)	0.003	81 (54.7)	–	598 (40.8)	<0.001
FET, *n* (%)	1853 (18.4)	34 (16)	–	183 (17.9)	–	20 (24.1)	–	99 (20.8)	–	25 (16.9)	–	428 (29.2)	–
Not recorded, *n* (%)	495 (4.9)	12 (5.7)	–	34 (3.3)	0.02	7 (8.5)	–	11 (2.3)	0.01	4 (2.7)	–	82 (5.5)	
Number of oocytes retrieved (mean ± SD)	7.4 ± 6.3	8.1 ± 9.4	–	8.1 ± 6.8	0.002	6.9 ± 6.8	–	7.8 ± 6.5	–	7.9 ± 5.9	–	6.0 ± 6.2	<0.001
Number of mature oocytes (mean ± SD)	5.7 ± 5.1	5.9 ± 7.8	–	6.2 ± 5.5	0.01	5.4 ± 5.6	–	5.9 ± 5.2	–	6.1 ± 4.9	–	4.7 ± 5.0	<0.001
Number of inseminated (mean ± SD)	6.2 ± 5.5	6.4 ± 8.3	–	6.7 ± 5.8	0.01	5.9 ± 5.9	–	6.2 ± 5.5	–	6.6 ± 5.1	–	5.1 ± 5.4	<0.001
Two pronuclei	4.1 ± 3.8	4.2 ± 6.3	–	4.2 ± 3.9	–	3.6 ± 3.8	–	4.1 ± 4.0	–	4.2 ± 3.8	–	3.4 ± 3.7	<0.001
Three pronuclei	0.2 ± 0.5	0.3 ± 0.8	–	0.2 ± 0.5	–	0.3 ± 0.7	–	0.2 ± 0.6	–	0.2 ± 0.5	–	0.2 ± 0.6	–
Total number of embryos (mean ± SD)	4.9 ± 3.9	5.4 ± 6.6	–	5.3 ± 4.1	0.003	4.9 ± 3.9	–	5.1 ± 4.0	–	5.1 ± 3.7	–	4.5 ± 3.7	<0.001
Fertilization rate[b]	(*n* = 7522)	(*n* = 157)		(*n* = 784)		(*n* = 56)		(*n* = 357)		(*n* = 114)		(*n* = 933)	
(mean ± SD)	0.73 ± 0.24	0.73 ± 0.23	–	0.71 ± 0.24	0.03	0.69 ± 0.24	–	0.72 ± 0.26	–	0.71 ± 0.25	–	0.74 ± 0.24	–
Number of embryos transferred, *n* (%)	(*n* = 10,062)	(*n* = 212)		(*n* = 1025)		(*n* = 83)		(*n* = 476)		(*n* = 148)		(*n* = 1467)	
0	1395 (13.9)	48 (22.6)	<0.001	128 (12.5)	–	12 (14.5)	–	60 (12.6)	–	20 (13.5)	–	183 (12.5)	–
1	3157 (31.4)	55 (25.9)	–	302 (29.5)	–	25 (30.1)	–	160 (33.6)	–	46 (31.1)	–	222 (15.1)	<0.001
2	5250 (52.2)	102 (48)	–	580 (56.6)	0.01	46 (55.4)	–	242 (50.8)	–	81 (54.7)	–	1021 (70)	<0.001
3	260 (2.6)	7 (3.3)	–	15 (1.5)	0.03	0	–	14 (2.9)	–	1 (0.7)	–	41 (2.4)	–
Number of embryos frozen	1.1 ± 2.5	1.9 ± 6.1	–	1.2 ± 2.5	–	0.9 ± 2.6	–	1.1 2.4	–	1.2 2.2	–	0.8 ± 2.2	<0.001

[a]Each ethnic group was compared with the reference group "White", only the statistically significant differences are reported.
[b]Fertilization rate is the number of embryos over the total number of oocytes retrieved.
FET = frozen embryo transfer; ICSI = intracytoplasmic sperm injection.

Table 3 Outcome data.[a]

	White (n = 10,062)	*Black (n = 212)*	*P-value*	*South Asian (n = 1025)*	*P-value*	*Chinese (n = 83)*	*P-value*	*Mixed (n = 476)*	*P-value*	*Other (n = 148)*	*P-value*	*Unknown (n = 1467)*	*P-value*
Implantation rate[b] (mean ± SD)	(*n* = 8667) 0.38 ± 0.46	(*n* = 164) 0.24 ± 0.39	<0.001	(*n* = 897) 0.38 ± 0.46	–	(*n* = 71) 0.35 ± 0.53	–	(*n* = 416) 0.33 ± 0.42	0.02	(*n* = 128) 0.30 ± 0.41	0.03	(*n* = 1284) 0.36 ± 0.44	–
Biochemical pregnancy rate, *n* (%)	4634 (46.1)	57 (26.9%)	<0.001	477 (46.5)	–	33 (39.8)	–	215 (45.2)	–	54 (36.5)	0.02	676 (46.1)	–
Clinical pregnancy rate, *n* (%)[c]	3970 (39.5)	48 (22.6)	<0.001	409 (39.9)	–	27 (32.5)	–	175 (36.8)	–	48 (32.4)	–	591 (40.3)	–
Pregnancy outcome, *n* (%):	*n* = 3930	*n* = 48		*n* = 395		*n* = 27		*n* = 170		*n* = 45		*n* = 590	
Live birth[d]	3492 (34.7)	42 (19.8)	<0.001	341 (33.3)	–	26 (31.3)	–	149 (31.3)	–	42(28.4)	–	530 (36.1)	–
Spontaneous abortion[e]	379 (9.5)	6 (12.5)	–	45 (11.0)	–	1 (3.7)	–	18 (10.3)	–	3 (6.3)	–	49 (8.3)	–
Termination[e]	20 (0.5)	0	–	3 (0.7)	–	0	–	1 (0.6)	–	0	–	3 (0.5)	–
Still birth[e]	15 (0.4)	0	–	4 (1.0)	–	0	–	1 (0.6)	–	0	–	4 (0.7)	–
Neonatal death[e]	24 (0.6)	0	–	2 (0.5)	–	0	–	1 (0.6)	–	0	–	4 (0.7)	–

[a]Each ethnic group was compared with the reference group "White", only the statistically significant differences are reported.
[b]Defined as the number of fetal hearts divided by the number of embryos transferred, per cycle.
[c]Defined as the presence of a gestational sac by ultrasound during first trimester.
[d]Expressed as a percentage of all cycles.
[e]Expressed as a percentage of clinical pregnancies.

significant when differences in age, body mass index, cause and duration of infertility, previous live birth, previous spontaneous abortion and number of embryos transferred were adjusted for; (OR 0.42 [0.25 to 0.70]; $P = 0.001$). Adjustment for differences in the same variables showed that the adjusted live birth rate in South Asian women was significantly lower than that in White women (OR 0.80 [0.65 to 0.99]; $P = 0.04$). The univariate and multivariate analyses for live birth for all ethnic groups are shown in **Table 4**.

The unadjusted results for clinical pregnancy for Black women compared with White women were similar to that of live birth: 22.6% and 39.5%, respectively ($P < 0.001$), and the difference remained after accounting for known confounders (OR 0.41 [0.25 to 0.67]; $P < 0.001$) (**Table 5**). The crude rates for implantation rate were also much lower for Black women compared with White women (0.24 versus 0.38).

South Asian women had similar clinical pregnancy rates as White women (39.9% versus 39.5% clinical pregnancy rates and 0.38 versus 0.38 for implantation rates). After adjustment in multivariate analyses for differences in confounding variables, still no difference was found in clinical pregnancy rates between South Asian women and White women (OR = 0.92 [0.75 to 1.12]). The univariate and multivariate analyses for clinical pregnancy for all ethnic groups is shown in **Table 5**.

The causes of infertility were grouped into tubal, ovulatory, male, unexplained and other. A sensitivity analysis was conducted to specifically look at whether fibroids could explain the effects on live birth outcome in the Black population. Fibroids were included in the heterogenous group termed "other" that included endometriosis and structural abnormalities. A separate variable for fibroids alone, adding this to the model including all the other covariates, had no effect on the relationship between Black ethnicity and lower live birth rates (Black OR 0.33 [0.14 to 0.77]; $P < 0.001$).

When exploring the live birth and clinical pregnancy rates for cryopreserved (frozen) cycles, the same multivariate analysis was conducted, using the same covariates on the frozen cycles alone. The same significant differences were found between the ethnic groups for live birth and clinical pregnancy outcomes in data from the frozen cycles as we did for the overall analysis (data not shown).

Discussion

Main findings

Results show significant disparities between ethnic groups for IVF outcomes.

Both Black and South Asian populations showed a statistically significant reduced chance of live birth after adjustment for confounding factors, which was consistent across the analyses of both fresh and frozen cycles together and individually. When exploring clinical pregnancy outcome, the Black population once again showed a statistically significant reduced chance of clinical pregnancy; furthermore, implantation rates were much lower for Black women than White women. Interestingly, when looking at implantation rates and clinical pregnancy rates for the South Asian population, no statistically significant difference was observed compared with White women. This could suggest that, although the South Asian population have a similar chance of achieving a pregnancy as

Table 4 Univariate and multivariate analyses for live birth.

Ethnic group	Number of cycles	Univariate analysis		Multivariate analysis[a]	
		OR (95% CI)	P-value	OR (95% CI)	P-value
White	10062	Reference		Reference	
South Asian	1025	0.94 (0.82 to 1.08)	NS	0.80 (0.65 to 0.99)	0.04
Black	212	0.47 (0.33 to 0.65)	<0.001	0.42 (0.25 to 0.70)	0.001
Chinese	83	0.86 (0.54 to 1.4)	NS	1.03 (0.52 to 2.01)	NS
Mixed	476	0.86 (0.70 to 1.05)	NS	0.88 (0.67 to 1.15)	NS
Other	148	0.75 (0.52 to 1.07)	NS	0.70 (0.41 to 1.17)	NS
Not stated	1467	1.07 (0.95 to 1.19)	NS	0.61 (0.41 to 0.93)	0.02

[a]Adjusted for age, body mass index, duration of infertility, cause of infertility, previous live birth, previous spontaneous abortion and number of embryos transferred.
NS = not statistically significant.

Table 5 Univariate and multivariate analyses for clinical pregnancy.

Ethnic group	Number of cycles	Univariate analysis		Multivariate analysis[a]	
		OR (95% CI)	P-value	OR (95% CI)	P-value
White	10062	Reference		Reference	
South Asian	1025	1.02 (0.89 to 1.16)	NS	0.92 (0.75 to 1.12)	NS
Black	212	0.45 (0.33 to 0.62)	<0.001	0.41 (0.25 to 0.67)	<0.001
Chinese	83	0.74 (0.47 to 1.17)	NS	0.92 (0.47 to 1.80)	NS
Mixed	476	0.89 (0.74 to 1.08)	NS	0.86 (0.66 to 1.13)	NS
Other	148	0.74 (0.52 to 1.04)	NS	0.68 (0.41 to 1.12)	NS
Not stated	1467	1.04 (0.93 to 1.16)	NS	0.62 (0.42 to 0.92)	0.02

[a]Adjusted for age, body mass index, duration of infertility, cause of infertility, previous live birth, previous spontaneous abortion and number of embryos transferred.
NS = not statistically significant.

the White population, they are more likely to lose the pregnancy (i.e. have a higher spontaneous abortion rate), resulting in a lower chance of live birth. This is consistent with data from a systematic literature review presented recently at the American Society for Reproductive Medicine, which looked at the relationship between ethnicity and spontaneous abortion (Harb et al., 2014).

Differences in findings were observed between unadjusted and adjusted estimates in our analyses. These differences have arisen because of clear differences in the characteristics of women from different ethnic groups who underwent infertility treatment (**Tables 1** and **2**). As South Asian women and those with unstated ethnicity had fewer risk factors than White women, adjusting for the risk factors increased the difference between these groups (**Tables 4** and **5**).

Comparison of results with existing literature

A literature review and meta-analysis were conducted to compare our results with that of previous studies. Sixteen comparable studies investigated the effect of ethnicity on IVF outcome (Mahmud et al., 1995; Lashen et al., 1999; Sharara and McClamrock, 2000; Nichols et al., 2001; Bendikson et al., 2005; Purcell et al., 2007; Jayaprakasan et al., 2014; Dayal et al., 2009; Shahine et al., 2009; Fujimoto et al., 2010; Mc-Carthy Keith et al., 2010; Seifer et al., 2010; Csokmay et al., 2011; Shuler et al., 2011; Sharara et al., 2012). All papers used data for non-donor cycles, and first treatment cycles only were included. The process of the literature search, table of study characteristics and table of demographic data are presented in **Supplementary Figure S1**, **Supplementary Table S1** and **Supplementary Table S2**, respectively. The quality of the studies was assessed using the Newcastle Ottawa Scale (Higgins et al., 2011) as shown in **Supplementary Table S3**.

Data from eight studies (Sharara and McClamrock, 2000; Nichols et al., 2001; Bendikson et al., 2005; Seifer et al., 2008, 2010; Dayal et al., 2009; Mc-Carthy Keith et al., 2010; Jayaprakasan et al., 2014) were combined to compare the Black population with a White population for live birth, clinical pregnancy rates, or both, after fresh cycle of treatment (**Supplementary Figure S2a** and **Supplementary Figure S2b**). Black women were found to have a statistically significant reduction in live births (OR 0.62 [0.55 to 0.71]; $P < 0.001$) and clinical pregnancy (OR 0.74 [0.64 to 0.87]; $P < 0.001$) compared with White women. These findings were in keeping with those of our cohort study.

Similarly to our cohort study, three papers calculated adjusted odds ratios (Seifer et al., 2008, 2010; Fujimoto et al., 2010) to attempt to adjust for confounding variables. These varied across the papers and included maternal age, body mass index, number of embryos transferred, diagnosis of male factor, endometriosis, polycystic ovary syndrome, diminished ovarian reserve, tubal factors, uterine factors and other factors. When these adjusted odds ratios were pooled, there was still a

reduced chance of live birth for Black women compared with White women (adjusted OR 0.70 [95% CI 0.57 to 0.83; $P<0.001$), consistent with the findings of our cohort study.

Three studies recorded data separately for frozen cycles (Seifer et al., 2008, 2010; Csokmay et al., 2011). These studies only investigated Black and White women. The meta-analysis results showed no difference in live birth or clinical pregnancy rates for Black women compared with White women: (OR 0.90 [0.75 to 1.07]) and (OR 0.94 [1.03 to 1.12]), respectively. This was not consistent with our cohort study, which showed that differences between ethnic groups remained statistically significant even when a sensitivity analysis was conducted for frozen cycles separately. With the results of the meta-analysis suggesting that Black women could do better with frozen cycles compared with fresh cycles this may be something to consider implementing into clinical practice. It also poses the question of whether there is something within the stimulation process of fresh cycles that Black women do not respond to as well as White women.

Eight studies compared Asian and White women (Mahmud et al., 1995; Lashen et al., 1999; Bendikson et al., 2005; Purcell et al., 2007; Shahine et al., 2009; Fujimoto et al., 2010; Sharara et al., 2012; Jayaprakasan et al., 2014) (**Supplementary Figure S3a** and **Supplementary Figure S3b**). These studies included women from South Asian and Chinese ethnic groups, and the meta-analysis showed that Asian women had a statistically significant reduction in both live birth (OR 0.67 [0.64 to 0.69]; $P<0.001$) and clinical pregnancy rate (OR 0.67 [0.65 to 0.70]; $P<0.001$) compared with White women. Of these eight studies, five specified a cohort of Indian or South Asian women (Jayaprakasan et al., 2014; Lashen et al., 1999; Mahmud et al., 1995; Shahine et al., 2009; Sharara et al., 2012). To directly compare the results of these five studies with our own cohort study, the data were meta-analysed in a specific 'South Asian' group. A statistically significant reduction in live birth and clinical pregnancy was found: (OR 0.66 [0.52 to 0.85]; $P=0.001$) and (OR 0.65 [0.47 to 0.90]; $P=0.008$), respectively (**Supplementary Figure S4a** and **Supplementary Figure S4b**). The reduced live birth rate is consistent with the findings of our cohort study. Our cohort study did not find a significant difference between South Asian and White women for clinical pregnancy rate, as discussed earlier, although the confidence interval on our estimate was wide and was compatible with an effect of the magnitude observed.

Given the UK population of our cohort study, we did not specifically account for the Hispanic population. As most of the studies in the search originated from the USA, the Hispanic population was frequently included. The findings for the Hispanic population were consistent with those for Black and Asian women showing a statistically significant reduction in live birth and clinical pregnancy rate compared with a White population (OR 0.86 [0.82 to 0.90]; $P<0.001$) and (OR 0.89 (0.85 to 0.93); $P<0.001$), respectively (**Supplementary Figure S5a and Figure S5b**). Only one of the four papers (Fujimoto et al., 2010) calculated an adjusted odds ratio for the live birth outcome. They adjusted for maternal age, number of embryos transferred and diagnosis of male factor, endometriosis, polycystic ovary syndrome, diminished ovarian reserve, tubal factors, uterine factors and other factors. This result was consistent in showing that the Hispanic population have a lower live birth rate compared with White women (adjusted OR 0.87 [95% CI 0.79 to 0.96]; $P=0.005$).

The data from both our cohort study and meta-analysis of existing studies shows that Black women and South Asian women have the poorest outcomes after IVF treatment. These differences could potentially be explained by the different diagnoses of infertility seen in different ethnic populations. Nine of the 16 papers (Sharara and McClamrock, 2000; Nichols et al., 2001; Bendikson et al., 2005; Seifer et al., 2008, 2010; Dayal et al., 2009; Fujimoto et al., 2010; Mc-Carthy Keith et al., 2010; Csokmay et al., 2011) found that Black women have a statistically significantly higher likelihood of tubal, uterine factor, or both, compared with White women, whereas White women were found to be more likely to have a diagnosis of endometriosis. Polycystic ovary syndrome was found to be more common among Asians than White women (Lashen et al., 1999; Sharara et al., 2012). Furthermore, a statistically significantly increased duration of infertility was fond among Asian women compared with White women (Lashen et al., 1999; Mahmud et al., 1995).

In our cohort study, we were able to adjust for cause of infertility. It is well known that fibroids are more common among the Black population and so would be the obvious explanation for the lower live birth rates seen in Black women. In our analysis, fibroids were adjusted for within a heterogenous group of infertility termed 'other' which included endometriosis, structural abnormalities and multiple fibroids. A sensitivity analysis adjusting for fibroids specifically maintained a lower live birth rate for Black women. Therefore, it is unlikely that causes of infertility alone can explain the differences in live birth seen across ethnic groups. In addition, findings were inconsistent across the existing papers for any differences in age and body-mass index for each ethnicity (**Supplementary Table S2**), and so this is also not likely to explain the differences seen in live birth or clinical pregnancy rates.

Strengths and limitations

One of the main strengths of our cohort study is the sample size. With the benefit of this large sample size, the size of the ethnic groups were large enough to analyse individually, thus allowing for detailed exploration into the effects on specific racial groups. Another strength is the specificity of the ethnic groups. No study to date has been able to analyse data for specific ethnic groups in detail. The largest US studies (Seifer et al., 2008, 2010) compared only Black women with White women. Other studies (Bendikson et al., 2005; Fujimoto et al., 2010; Mc-Carthy Keith et al., 2010) only used four main ethnic groups (Black, Asian, Hispanic and White), which meant combining certain racial groups like South Asian with Chinese, who are genetically different and so would not necessarily behave in the same way. Furthermore, no study has previosuly accounted for the mixed race population. Owing to the large number of variables recorded within the database, a large majority of the known confounders in the multivariate analysis, could be accounted for, which other studies previously have failed to do. To the best of our knowledge, this is also the first study on this topic to have carried out a meta-analysis of all existing literature.

We acknowledge significant unequal distribution of cycles among each ethnic group; furthermore, a substantial number of patients ($n=1467$) have not stated ethnicity. This group

constitutes more than 10% of the study population, plus all the ethnic minority groups are smaller than this 'not stated' group and so this may have influenced the data and added bias to the results.

A further limitation of the study is that we were unable to account for smoking status or alcohol consumption. It could be that these factors play a role in the lower pregnancy success rates seen in certain ethnic groups. In addition, we were unable to adjust for ovarian reserve or embryo quality as known confounders when performing multivariate analysis; this was because of the insufficient numbers recorded. It could be argued that the difference in IVF success rates may be influenced primarily by socioeconomic factors, such as lack of access to medical treatment leading to higher age at first encounter. Unfortunately, our cohort study was unable to explore socio-economic factors in detail. Furthermore, the large majority of the patient population from our cohort study were non-NHS patients paying for their own treatment, which adds a population bias.

In conclusion, research on assisted conception has predominantly been carried out among cohorts of White women. Studies to date have found inconclusive results for assisted conception success rates among women from different ethnic backgrounds. This cohort study, in combination with our meta-analysis, provides robust evidence for the hypothesis that an association exists between ethnic background and IVF success. Moreover, this does not seem to be easily explained by the commonly known confounders. The findings of this study should prompt investigation into the mechanisms underpinning such disparities to allow modification of laboratory, clinical practice, or both, to improve IVF outcome for all ethnic groups. Furthermore, there needs to be careful consideration of whether such information should be provided to patients as part of pre-treatment counselling as, although ethnicity is a factor that patients are unable to change, it may have implications on their decision-making.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2015.05.015.

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