Ethnic group and reason for assisted reproductive technology failure: analysis of the Human Fertilisation and Embryology Authority registry data from 2017 to 2018

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Objective: To understand how the risk of different assisted reproductive technology (ART) failure types varies by ethnic group and explore the role of mediation by maternal age and suspected etiology.
Design: An observational study of 48,750 women who undertook treatment with ART in the United Kingdom between January 2017 and December 2018.
Setting: The Human Fertilisation and Embryology Authority national ART registry of the United Kingdom.
Patient(s): Women who commenced a first cycle of ART for the purpose of primary fresh embryo transfer using their own oocytes were included.
Intervention(s): Maternal ethnic group.
Main Outcome Measure(s): The ART failure types were modeled on the maternal ethnic group using the Poisson regression to produce relative risks (RRs) with 95% confidence intervals. The potential indirect effects of maternal age and etiology of subfertility were estimated, and the RRs with 95% confidence intervals were produced.
Result(s): Black women were at greater risk of treatment failure with respect to live birth than women who were white: cycle cancellation, RR of 2.15 (1.78–2.62); failed fertilization, RR of 2.36 (1.90–2.93); unintended freeze-all, RR of 1.71 (1.43–2.05); failed implantation, RR of 1.23 (1.12–1.34); and pregnancy loss, RR of 1.38 (1.15–1.64). Women who were Asian were at moderately increased risk: RRs of 1.31 (1.17–1.47), 1.60 (1.42–1.80), 1.25 (1.14–1.38), 1.11 (1.07–1.16), and 1.13 (1.03–1.23), across the same outcomes, respectively. Inequality may have been reduced had women of all ethnicities initiated treatment at the same age.
Conclusion(s): Black women were at greatest risk of all failure types, and women who were Asian were at intermediate risk compared with women who were white. Some of the risks among women who were black may be mediated by maternal age. (Fertil Steril® 2023;119:241-9. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Health inequality, ethnicity, assisted reproduction, competing risks, epidemiology

The chance of achieving live birth after assisted reproductive technology (ART), either in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), differs by a woman's ethnic background (1). Women who are Asian or black have lower live birth rates than those who are white, and disparities exist across the fertility pathway (2, 3). Ethnicity is a complex exposure that could affect a woman's chance of live birth for different reasons: socioeconomic disadvantage; poorer access to quality healthcare; or different health behaviors and healthcare expectations (4). Health inequalities arise from differences in the socioeconomic and

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environmental conditions of health between groups (5). Biologic differences may also be acquired owing to socioeconomic and environmental disadvantage; however, ethnicity is not itself a "genetic" explanation for health inequality. The reasons for differences must be considered carefully to be explained and addressed (6, 7). What we need to better understand is how differences arise.

The ART treatment pathway involves several stages. A typical cycle begins with ovarian stimulation and oocyte collection; if successful, the oocytes are fertilized spontaneously or by ICSI; if successful, at least 1 embryo is created of sufficient quality, and a fresh embryo transfer is scheduled (unless precluded by ovarian hyperstimulation syndrome or any other external factors); if successful, a healthy and normally sited pregnancy occurs and leads to live birth. This study aimed to characterize differences in outcomes after ART by ethnic background, by simultaneously estimating the risk of the different failure types and exploring how the association between ethnicity and these outcomes could be mediated. We hypothesize that the risk of failure at each stage of the treatment pathway differs between ethnic groups and maternal age and etiology of subfertility may act as mediators.

MATERIALS AND METHODS

Population

The Human Fertilisation and Embryology Authority (HFEA) maintains a registry of licensed fertility treatment in the United Kingdom. Data are submitted to the HFEA in accordance with the UK law. This study makes secondary use of the HFEA's anonymized data set on ART conducted in 2017–2018, which contains unlinked data with respect to ART cycle (8). Data on women aged <18 years or >50 years were not available in the anonymized data set because of the risk of reidentification. The inclusion criteria for this study were women who underwent their first cycle of ART for the purpose of primary fresh embryo transfer. Surrogate pregnancies and planned freeze-all cycles for any reason, including for preimplantation genetic testing, were excluded.

Primary Outcome

The outcome was a multinomial outcome representing ART failure type, comprised of mutually exclusive categories of cycle cancellation, where ovarian stimulation or monitoring was commenced with the intention to treat but follicular aspiration did not occur; failed fertilization, defined as total failure of fertilization of all collected oocytes; unintended freeze-all, where created embryos were cryopreserved and fresh embryo replacement did not occur; failed implantation, defined as a negative pregnancy test result after embryo replacement; pregnancy loss, defined as any pregnancy that did not result in at least 1 live birth from all causes (9); and live birth greater than 24 weeks of gestation, which was the reference category.

Statistical Analyses

Descriptive statistics for demographic and treatment characteristics were calculated according to the maternal ethnic group, with frequencies and proportions for the categorical data. The data in the anonymized data set were largely categorical for the purpose of data minimization and anonymization. The main exposure of interest was maternal ethnicity defined as per the HFEA anonymized data set (Asian, black, mixed, other, and white). These self-reported ethnic groups are consistent with the Office for National Statistics high-level ethnic groups used for the Census of England and Wales (10). In the data set, women with missing data on ethnic group were combined with women whose ethnic group was one of the true "other" groups. The main analysis preserved the "other" ethnic group.

The ART failure type was modeled on the ethnic group using the Poisson regression with robust standard errors to produce relative risks (RRs) with 95% confidence intervals. Live birth was used as the baseline risk group in each model. Relative risks were estimated with adjustment for year of treatment (2017 and 2018), and sequential adjustment was made for maternal age at treatment (18–34, 35–37, 38–39, 40–42, and 43–50 years) and then maternal age and suspected etiology (endometriosis, male factor, ovulatory, tubal, "no male partner" [representing women who were single or women in same-sex relationships who otherwise had no diagnosed cause for subfertility], and "unreported" [with neither an assigned cause nor "unexplained" categorization]). In the United Kingdom, the investigation and diagnosis of the suspected etiology of subfertility are based on national guidance (11). Neither data on diminished ovarian reserve nor uterine, including fibroid, causes were presented in the HFEA data set. The main analysis included women with missing data on suspected etiology as an "unreported" category on the basis that may represent other causes that were not reported in the anonymized data set. Further adjustment was not made for the type of ART used (IVF or ICSI) because of the inclusion of women whose oocyte collection failed.

To understand the potential mediating pathways between maternal ethnicity and ART outcome, a mediation analysis was conducted to explore the role of maternal age and assigned etiology of subfertility, on the basis of the same model, using the procedure outlined by Kohler et al. (12). This mediation analysis was based on the weak assumptions notion of ethnicity posited by VanderWeele and Robinson (13), on the basis of the time-ordered nature of ethnic group at birth and from the perspective of the manipulability of the mediator. Here, the "total effect" represented the broad range of measured and unmeasured pathways between the ethnic group and ART outcome; "direct effect" represented the remaining inequality outside of the mediated pathway after accounting for equalization of ethnic groups with respect to either age or etiology; "indirect effect" represented the potentially mediated inequality. The proportions of total "effects" mediated by the indirect pathway are reported although reference should be made to the respective 95% confidence intervals. We assume that unmeasured socioeconomic and lifestyle variables lie on the causal pathway between the ethnic group and maternal age/etiology, ethnic group and ART outcome, and maternal age/etiology and ART outcome; therefore, we assume that these associations are not subject to unmeasured confounding but that there are other unmeasured mediating pathways.

Sensitivity Analyses

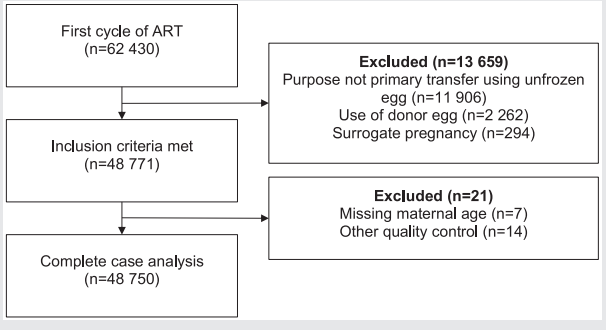
The proportions and patterns of missing data were examined. If the proportion of cases with missing data exceeded 5%, a multiple imputation procedure was conducted. Because the "other" ethnic group contained both women who were correctly categorized and women whose ethnic group was missing, we tested sensitivity to missingness. All women in the "other" ethnic group were, therefore, set to missing and their ethnic group was imputed. Similarly, because women with no reported etiology may include those who belong to a distinct but unreported group as well as those who belong to a reported group with missing data, we tested sensitivity to missing etiology. In a separate sensitivity analysis, women with missing suspected etiology were set to missing and imputed. Multiple imputation procedures were implemented using the multiple imputation by chained equations algorithm in Stata version 16 (14). Auxiliary variables were tested and included if associated with both missingness and the known values of variables with missing data to strengthen the missing at random assumption. A total of 50 data sets were imputed, ensuring relative efficiencies >99% and Monte Carlo error estimates <10% of standard errors for all variables. Additionally, we tested sensitivity to adjustment for type of ART (IVF or ICSI), from the failed fertilization stage onward.

Statistical analyses were performed using Stata version 16 (14).

Ethical Approval

This was a secondary analysis of the publicly available HFEA anonymized data set. The information available in this data set is restricted, and data minimization techniques have been used to reduce the risk of reidentification. The HFEA has permission to collect and publish the data. No additional ethical approval was required for this analysis. Institutional review board permission was not required for the use of this public data set.

FIGURE 1



Selection criteria. The categories of the excluded participants were overlapping and were not mutually exclusive. ART = assisted reproductive technology.

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RESULTS

A total of 62,430 first cycles of ART were included in the registry for 2017–2018. After the exclusion of 13,680 women, 48,750 women met the inclusion criteria and were included in the main analyses. The inclusion and exclusion criteria and proportion of missing data are shown in Figure 1. Among those with complete data, 13,817 (13,817/48,750, 28.3%) women had at least 1 live birth.

Characteristics of the Included Women

The characteristics of included women are shown in Table 1. The ethnic compositions of the sample were the following: Asian, 5,501 (11.3%); Black, 1,155 (2.4%); mixed ethnicity, 783 (1.6%); "other" ethnic background; 7,746 (15.9%); and White, 33,565 (68.9%). Half the women were between the ages of 18 and 34 years, and the leading assigned cause was male factor subfertility. Overall, a greater proportion of Asian women commenced ART at an earlier age and had a diagnosis of ovulatory subfertility, and a lower proportion had tubal subfertility. A greater proportion of black women commenced ART at a later age and had tubal subfertility; however, these women had the lowest prevalence of ovulatory subfertility. Regarding treatment outcomes, a greater proportion of women who were black had no oocytes collected, failed fertilization, unintended freeze-all, and failed implantation, relative to all other ethnic groups, and the second highest proportion of pregnancy loss behind the "other" group. The proportion of women who achieved a live birth was lowest among women who were black and greatest among women who were white.

Risk of ART Failure

The RRs for ethnic groups, compared with women who were white, for each type of failure relative to live birth, are shown in Table 2. Women who were black were at greatest risk at each stage of treatment compared with white women, with approximately twice the risk of cycle cancellation (RR, 2.15 [1.78–2.62]), failed fertilization (RR, 2.36 [1.90–2.93]), and unintended freeze-all (RR, 1.71 [1.43–2.05]) and an increased risk of failed implantation (RR, 1.23 [1.12–1.34]) and pregnancy loss (RR, 1.38 [1.15–1.64]), relative to live birth and compared with white women. Women who were Asian were at moderately increased risk earlier in the pathway and at mildly increased risk of failed implantation and pregnancy loss, compared with white women. No inequality was observed among women in the "mixed" or "other" ethnic groups compared with those in the white group. Among women who were Asian, who were younger, the estimates slightly increased in magnitude after adjustment for maternal age. Among women who were black, who were older, the estimates decreased in magnitude after adjustment for maternal age. There was less difference after adjustment for indication for ART.

For comparison with studies in which the risk of live birth after embryo transfer was estimated, when the baseline risk was women who had embryo transfer and did not achieve live birth, the chance of live birth was lowest among women

TABLE 1

Baseline characteristics according to maternal ethnicity.

	Ethnic group					
	Asian	Black	Mixed	Other	White	Total
Variable	**5,501 (11.3)**	**1,155 (2.4)**	**783 (1.6)**	**7,746 (15.9)**	**33,565 (68.9)**	**48,750 (100.0)**
Maternal age, y, n (%)						
18–34	3,076 (55.9)	454 (39.3)	358 (45.7)	3,413 (44.1)	16,734 (49.9)	24,035 (49.3)
35–37	1,115 (20.3)	221 (19.1)	189 (24.1)	1,826 (23.6)	7,691 (22.9)	11,042 (22.7)
38–39	658 (12.0)	199 (17.2)	101 (12.9)	1,186 (15.3)	4,539 (13.5)	6,683 (13.7)
40–42	492 (8.9)	170 (14.7)	106 (13.5)	968 (12.5)	3,619 (10.8)	5,355 (11.0)
43–50	160 (2.9)	111 (9.6)	29 (3.7)	353 (4.6)	982 (2.9)	1,635 (3.4)
Indication, n (%)						
Endometriosis	349 (6.3)	56 (4.9)	52 (6.6)	477 (6.2)	2,104 (6.3)	3,038 (6.2)
Male factor	1,791 (32.6)	368 (31.9)	262 (33.5)	2,462 (31.8)	11,711 (34.9)	16,594 (34.0)
Ovulatory	835 (15.2)	88 (7.6)	92 (11.8)	785 (10.1)	3,959 (11.8)	5,759 (11.8)
Tubal factor	453 (8.2)	188 (16.3)	86 (11.0)	711 (9.2)	3,445 (10.3)	4,883 (10.0)
Social	40 (0.7)	43 (3.7)	40 (5.1)	202 (2.6)	1,673 (5.0)	1,998 (4.1)
Unexplained	1,973 (35.9)	322 (27.9)	245 (31.3)	2,880 (37.2)	10,910 (32.5)	16,330 (33.5)
Missing	658 (12.0)	210 (18.2)	103 (13.2)	987 (12.7)	3,770 (11.2)	5,727 (11.8)
Oocytes collected, n (%)						
0	351 (6.4)	108 (9.4)	39 (5.0)	430 (5.6)	1,896 (5.7)	2,824 (5.8)
1–5	1,185 (21.5)	305 (26.4)	172 (22.0)	1,623 (21.0)	7,561 (22.5)	10,846 (22.3)
6–10	1,722 (31.3)	319 (27.6)	252 (32.2)	2,353 (30.4)	10,850 (32.3)	15,496 (31.8)
11–15	1,220 (22.2)	197 (17.1)	168 (21.5)	1,743 (22.5)	7,496 (22.3)	10,824 (22.2)
>15	1,023 (18.6)	226 (19.6)	152 (19.4)	1,597 (20.6)	5,762 (17.2)	8,760 (18.0)
Embryos created, n (%)						
0	684 (12.4)	194 (16.8)	81 (10.3)	788 (10.2)	3,335 (9.9)	5,082 (10.4)
1–5	2,460 (44.7)	548 (47.5)	349 (44.6)	3,379 (43.6)	15,112 (45.0)	21,848 (44.8)
6–10	1,607 (29.2)	266 (23.0)	232 (29.6)	2,303 (29.7)	10,383 (30.9)	14,791 (30.3)
>10	750 (13.6)	147 (12.7)	121 (15.5)	1,276 (16.5)	4,735 (14.1)	7,029 (14.4)
Embryos transferred, n (%)						
0	1,183 (21.5)	316 (27.4)	153 (19.5)	1,302 (16.8)	6,125 (18.3)	9,079 (18.6)
1	3,089 (56.2)	521 (45.1)	430 (54.9)	4,216 (54.4)	20,007 (59.6)	28,263 (58.0)
2	1,200 (21.8)	303 (26.2)	192 (24.5)	2,043 (26.4)	7,198 (21.4)	10,936 (22.4)
3	29 (0.5)	15 (1.3)	8 (1.0)	185 (2.4)	235 (0.7)	472 (1.0)
Cycle cancellation, n (%)	351 (6.4)	108 (9.4)	39 (5.0)	430 (5.6)	1,894 (5.6)	2,822 (5.8)
Failed fertilization, n (%)	331 (6.0)	86 (7.5)	42 (5.4)	354 (4.6)	1,426 (4.3)	2,239 (4.6)
Unintended freeze-all, n (%)	499 (9.1)	122 (10.6)	72 (9.2)	508 (6.6)	2,777 (8.3)	3,978 (8.2)
Failed implantation, n (%)	2,407 (43.8)	508 (44.0)	336 (42.9)	3,350 (43.3)	13,742 (40.9)	20,343 (41.7)
Pregnancy loss, n (%)	600 (10.9)	127 (11.0)	69 (8.8)	928 (12.0)	3,827 (11.4)	5,551 (11.4)
Live birth, n (%)	1,313 (23.9)	204 (17.7)	225 (28.7)	2,176 (28.1)	9,899 (29.5)	13,817 (28.3)

Note: The denominators for reported proportions are the ethnic group totals, or whole sample total, found at the top of each column and not women who progressed to the previous treatment stage. The indications for treatment are not mutually exclusive, except for the distinct category of unexplained subfertility.

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who were black (RR, 0.67 [0.59–0.77]) and decreased among women who were Asian (RR, 0.84 [0.80–0.89]) or in the "other" category (RR, 0.94 [0.89–0.98]), compared with women who were white.

Mediation Analyses

We estimated what proportion of the association between ethnicity and failure type may be eliminated if age at treatment initiation was equalized (Table 3). Among women who were black, approximately 27% of the association between ethnicity and cycle cancellation was mediated by maternal age, 28% for failed fertilization, 5% for unintended freeze-all, 31% for failed implantation, and 19% for pregnancy loss. There was no evidence of mediation via the positively identified suspected etiologies of subfertility for any ethnic group.

Sensitivity Analyses

The effect of further adjustment for the type of ART (IVF or ICSI) on outcome was considered from the point of failed fertilization onward. Although a greater proportion of women who were black received ICSI, the findings were insensitive to adjustment.

Missing Data

For observations within our inclusion criteria, suspected etiology was missing for 5,728 (11.8%) women, and maternal age was missing for 7 women (<0.1%). Missing etiology was associated with maternal and paternal age, maternal and partner ethnicity, and treatment characteristics and outcomes. Women who were black or of mixed ethnicity, compared with women who were white, were more likely to have missing etiology. The findings differed only negligibly for outcomes for the earlier failure types in the first multiple

TABLE 2

Relative risk ratios for the assisted reproductive technology failure types for maternal ethnicity.

Ethnic group	Cycle cancellation RR (95% CI) (n = 2,822)	Failed fertilization RR (95% CI) (n = 2,239)	Unintended freeze-all RR (95% CI) (n = 3,978)	Failed implantation RR (95% CI) (n = 20,343)	Pregnancy loss RR (95% CI) (n = 5,551)
Maternal ethnicity					
Asian	1.31 (1.17–1.47)	1.60 (1.42–1.80)	1.25 (1.14–1.38)	1.11 (1.07–1.16)	1.13 (1.03–1.23)
Black	2.15 (1.78–2.62)	2.36 (1.90–2.93)	1.71 (1.43–2.05)	1.23 (1.12–1.34)	1.38 (1.15–1.64)
Mixed	0.92 (0.67–1.26)	1.25 (0.92–1.69)	1.10 (0.87–1.39)	1.03 (0.92–1.15)	0.84 (0.66–1.07)
Other	1.02 (0.92–1.14)	1.11 (0.99–1.25)	0.87 (0.79–0.96)	1.04 (1.00–1.08)	1.07 (1.00–1.15)
White	1	1	1	1	1
+Adjustment for maternal age					
Asian	1.35 (1.20–1.51)	1.62 (1.44–1.82)	1.26 (1.14–1.38)	1.13 (1.08–1.18)	1.16 (1.07–1.27)
Black	1.64 (1.35–1.99)	1.69 (1.36–2.11)	1.65 (1.38–1.98)	1.15 (1.05–1.25)	1.28 (1.07–1.52)
Mixed	0.91 (0.66–1.24)	1.18 (0.87–1.61)	1.10 (0.87–1.39)	1.01 (0.90–1.12)	0.84 (0.66–1.07)
Other	0.96 (0.87–1.07)	1.04 (0.93–1.17)	0.87 (0.79–0.95)	1.02 (0.98–1.06)	1.03 (0.96–1.11)
White	1	1	1	1	1
+Adjustment for indication for IVF					
Asian	1.35 (1.20–1.51)	1.62 (1.43–1.82)	1.21 (1.10–1.33)	1.13 (1.08–1.18)	1.16 (1.06–1.26)
Black	1.61 (1.33–1.96)	1.63 (1.30–2.03)	1.64 (1.37–1.96)	1.14 (1.04–1.25)	1.28 (1.07–1.53)
Mixed	0.92 (0.67–1.26)	1.18 (0.87–1.60)	1.09 (0.86–1.38)	1.01 (0.90–1.12)	0.84 (0.66–1.07)
Other	0.99 (0.89–1.09)	1.04 (0.93–1.17)	0.87 (0.79–0.95)	1.01 (0.98–1.05)	1.03 (0.96–1.11)
White	1	1	1	1	1

Note: An RR greater than 1 signifies a greater risk of the outcome occurring among an ethnic group than the baseline risk among women who were white. Similarly, an RR of 1 signifies equality for the outcome compared with women who were white, and an RR lower than 1 signifies a lower risk. The uppermost results are adjusted for year of treatment only. The middle results are additionally adjusted for maternal age, and the lowermost results are additionally adjusted for suspected etiology. CI = confidence interval; IVF = in vitro fertilization; RR = relative risk.

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imputation procedure and were insensitive to inclusion of women with missing data on etiology.

Women in the "other" ethnic group comprised 15.9% of the sample. Compared with summary data reported elsewhere, approximately 85% of this group had missing data on the ethnic group (1). After multiple imputation, a disproportionate number of women in the "other" group were assigned to the Asian, black, or mixed ethnic groups, as opposed to the white ethnic group. The baseline characteristics drawn from the first imputed data set are shown in Supplemental Table 1 (available online) as an example. The results from this second multiple imputation procedure are shown in Supplemental Table 2. The estimates were overall insensitive to reapportionment of the "other" group.

DISCUSSION

The initiation of treatment with ART differed by ethnic group. A greater proportion of women who were Asian initiated IVF, and a lower proportion of women who were black initiated IVF, compared with the UK-wide ethnic composition (10). Outcomes across the fertility pathway varied according to ethnic group. We estimated the risk of failure during the first cycle of ART and observed that women who were Asian or black had a greater risk of cycle cancellation, failed fertilization, unintended freeze-all, implantation failure, and pregnancy loss. Women who were black initiated treatment later in life. We found that had women who were black initiated treatment at the same age as women who were white, approximately a quarter of the differences for most outcomes may have been eliminated.

The strengths of this study are that we characterized health differences for points of failure across the fertility pathway. We minimized bias by considering the likely mediators of the association between ethnicity and outcome, so as not to eliminate the effects of mediators that may lie on the causal pathway. Therefore, we explored the possible contribution of maternal age, which is itself a complex socioeconomic and biologic risk factor. We reported missingness and its handling transparently and ensured that women with missing data were not excluded, considering different conditions for missing data. Given the heterogeneous population, the findings are generalizable to service users in the United Kingdom and are comparable to other high-income reproductive care settings.

We studied the first cycle of treatment given the clustered but unlinked nature of the HFEA anonymized data set. This enabled us to study differences between ethnic groups, although we could not determine whether treatment strategies may alter outcomes beyond the first cycle, once treatment characteristics are known. Additionally, the use of the first cycle meant that a greater proportion of women were eligible to receive government funded treatment, subject to local clinical criteria and national guidance on age and family situation being met. This restriction allowed us to partially control for the affordability of treatment.

In the HFEA anonymized data set, high-level Office for National Statistics categories were used to reduce the risk of reidentification. These were preserved in the analysis. A weakness was the inclusion of women with unreported ethnicity within the "other" category. Missing ethnic group was reported in summary data on fresh cycles performed in

TABLE 3

Total and direct effects between maternal ethnicity and failure types.

	Total	Direct	Indirect
Ethnic group	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
	Cycle cancellation		
Asian	1.32 (1.18–1.48)	1.35 (1.20–1.51)	0.98 (0.91–1.05), $P=.50$
Black	1.98 (1.63–2.40)	1.64 (1.35–1.99)	1.21 (1.13–1.29), $P<.001$
Mixed	0.92 (0.67–1.26)	0.91 (0.66–1.24)	1.01 (0.95–1.08), $P=.72$
Other	1.01 (0.91–1.12)	0.96 (0.87–1.07)	1.05 (0.98–1.12), $P=.29$
White	1	1	-
	Failed fertilization		
Asian	1.59 (1.41–1.79)	1.62 (1.44–1.82)	0.98 (0.90–1.06), $P=.63$
Black	2.07 (1.66–2.57)	1.69 (1.26–2.11)	1.22 (1.13–1.33), $P<.001$
Mixed	1.23 (0.90–1.67)	1.18 (0.87–1.61)	1.04 (0.96–1.12), $P=.37$
Other	1.10 (0.98–1.23)	1.04 (0.93–1.17)	1.05 (0.97–1.14), $P=.24$
White	1	1	-
	Unintended freeze-all		
Asian	1.26 (1.14–1.38)	1.26 (1.14–1.38)	1.00 (0.98–1.02), $P=.97$
Black	1.70 (1.41–2.03)	1.65 (1.38–1.98)	1.03 (1.00–1.05), $P=.02$
Mixed	1.10 (0.87–1.39)	1.10 (0.87–1.39)	1.00 (0.98–1.02), $P=.82$
Other	0.87 (0.79–0.96)	0.87 (0.79–0.95)	1.00 (0.98–1.02), $P=.80$
White	1	1	-
	Failed implantation		
Asian	1.11 (1.07–1.16)	1.13 (1.08–1.18)	0.97 (0.96–1.00), $P=.12$
Black	1.22 (1.12–1.33)	1.15 (1.05–1.25)	1.06 (1.04–1.09), $P<.001$
Mixed	1.03 (0.92–1.15)	1.01 (0.90–1.12)	1.02 (1.00–1.04), $P=.03$
Other	1.04 (1.00–1.08)	1.02 (0.98–1.06)	1.02 (1.00–1.04), $P=.02$
White	1	1	-
	Pregnancy loss		
Asian	1.13 (1.04–1.23)	1.16 (1.07–1.27)	0.97 (0.93–1.01), $P=.12$
Black	1.35 (1.13–1.62)	1.28 (1.07–1.52)	1.06 (1.02–1.10), $P=.003$
Mixed	0.84 (0.66–1.07)	0.84 (0.66–1.07)	1.00 (0.96–1.04), $P=.95$
Other	1.07 (0.99–1.15)	1.03 (0.96–1.11)	1.03 (0.99–1.07), $P=.10$
White	1	1	-

Note: An RR greater than 1 signifies a greater risk of the outcome occurring among an ethnic group than the baseline risk among women who were white. Similarly, an RR of 1 signifies equality for the outcome compared with women who were white, and an RR lower than 1 signifies a lower risk. Total effect is the effect of maternal ethnicity on outcome by any pathway. Direct effect represents the potential effect of maternal ethnic group on outcome, excluding any effect mediated by maternal age. Indirect effect represents the potential effect exerted by ethnic group through maternal age. *P* values are presented for the indirect effects to aid interpretation. CI = confidence interval; RR = relative risk.

Henderson. Ethnic group and ART failure. Fertil Steril 2023.

2017 and 2018 released with the report "Ethnic Diversity in Fertility Treatment" (1). Ethnicity was missing for 12.7% of women for all fresh cycles during this period, whereas the true "other" ethnic group comprised only 2.6% of fresh cycles. Data may be routinely omitted; however, it is credible that ethnicity could be omitted for reasons due to that ethnic group itself. In the sensitivity analysis, the chance of imputing Asian, black, or mixed ethnic groups was greater than that of the white ethnic group. Women whose data were missing also had poorer outcomes. It is concerning that the quality of reporting could vary systematically but we are unable to explore the reasons further. Nevertheless, our overall findings were insensitive to recategorization of the "other/missing" ethnic category.

The overall chance of achieving a live birth in the first cycle in our sample was comparable to that of an earlier study of the HFEA registry, as well as findings from a meta-analysis of studies on ethnic group and reproductive outcomes (15, 16). The findings are also consistent with evidence from the Society for Assisted Reproductive Technology Clinical Outcome Reporting System registry in the United States, where lower live birth rates were observed among women who were black or Asian (17, 18). These studies identified a greater prevalence of tubal and uterine disease among women who were black, a greater cycle cancellation rate, and lower crude elective single embryo transfer, implantation, clinical pregnancy, and live birth rates. "Race" was a risk factor after adjustment for age and obstetric history, body mass index (BMI), etiology, measures of ovarian reserve, and within-cycle characteristics (18). We cannot provide direct comparison with these studies because of the different ethnic groups and different conceptualization of the causal pathway and available data. We did not identify any mediating role of tubal disease; however, we did not have data on fibroid disease. We presented the results before adjustment for maternal age and assigned etiology because these were hypothesized to lie on the causal pathway between ethnicity and ART outcome, whereas some studies have identified these as sources of confounding. Similarly, we did not adjust for earlier causes of ART failure but accounted for the multiple classes of ART failure with our outcome variable.

We found that a greater proportion of women who were black were older at their first cycle of ART and evidence that maternal age may mediate a portion of the association between ethnicity and multiple outcomes. The underlying contributors as to why women from 1 ethnic group may

commence ART later in life are likely complex and may include direct barriers, such as discrimination (19), or indirect barriers, such as socioeconomic situation (20). In the United Kingdom, restrictions on funding for ART are introduced from a maternal age of 40 years (11). Within our sample, 20% of women who were black had a maternal age of >40 years. A greater proportion of women who were black may, therefore, have self-funded or decided not to initiate treatment. As well as socioeconomic factors, systemic bias and cultural factors around decision-making may influence the initiation of treatment (21). A systematic review of qualitative studies identified lower health and fertility literacy, language barriers, faith-based barriers, cultural stigma and psychological distress, and a lack of trust as barriers to equitable fertility care (22). It is important to account for the distal causes of inequalities rather than assert that ethnicity itself is the explanation. Even where a cultural explanation has been identified, support and health education may overcome these barriers (23–25). That maternal age may mediate the risk at various treatment thresholds is biologically plausible given multiple mechanisms (26) affecting oocyte and embryo quantity and quality (27), as well as through lifestyle and socioeconomic pathways. We did not have detailed data on the full range of mediators to inform our mediation models. For maternal age, unmeasured risk factors are assumed likely to lie on the causal pathway between maternal age and treatment outcome. We do not assert that any difference because of maternal age is a direct biologic mechanism but a combination of all pathways. This analysis provides an understanding of how inequalities may change if women from different ethnic groups initiated treatment at the same age of women who were white. We did not identify any other studies that have investigated the potential mediating effect of maternal age for comparison. Ensuring that women from different ethnic backgrounds receive quality assessment of their reproductive needs, timely referral, and high-quality counseling from a fertility care provider may increase the chance of successful treatment. Conversely, we did not observe an association between Asian ethnicity and any failure types via age.

Despite tubal factor subfertility being thought to be more prevalent among women who are black, we did not find evidence of mediation via this pathway within the assumptions of this mediation model. This finding could be because of misclassification including the overdiagnosis of tubal disease in women who were black, as well as confounding. We did not have data on other comorbidities, smoking status, or BMI, which may be important when understanding the potential effect of underlying etiologies. Again, we, therefore, assume that variables between etiology and ART outcome lie on the causal pathway. This exploratory model should be interpreted cautiously because this may not be the case. Although unmeasured variables, such as BMI or smoking, may cause worse outcomes, they may also act on etiology causally, introducing confounding. However, if an unmeasured confounder were to act on etiology and ART outcome, then we would expect the mediated pathway to be overestimated, as opposed to underestimated (28). The role of etiology warrants further investigation, including the potential role of fibroid as well as tubal disease.

Studies have examined other potential explanations for the association between ethnicity and ART outcome. In the United States, inequality persisted between ethnicities even within strata of BMI (29). Another study attributed worse outcomes among women who were black to increased age, BMI, and tubal factor subfertility on the basis that these were risk factors in an ethnicity-specific sample, although this does not mean that these are not risk factors common to all women and they do not necessarily explain inequality (30). Women who were black were also found to be at greater risk of ovarian hyperstimulation syndrome, a risk factor for adverse outcome (31). Women who are black may face a double burden of delayed access to care followed by treatment, which, to optimize outcomes, also places them at risk of further complications (17).

Further research should include ongoing surveillance of outcomes according to ethnic background, enquiry into the determinants of health inequality, and the design of interventions to mitigate health inequality. Assisted reproductive technology care providers should audit and understand treatment patterns according to ethnic group within their populations and ensure complete data on ethnic group. A holistic approach considering social risk factors and barriers, including interpersonal and systemic bias, may identify opportunities to improve access to care.

In conclusion, this study identified inequalities across the ART pathway, with women who were black or Asian at greater risk all types of treatment failure. The disparity remains unexplained. For women who were black, some of the difference in risk may be mediated by maternal age at initiation of treatment, which is a modifiable risk factor. The distal determinants of reproductive health and decision-making require further characterization; however, potentially modifiable proximal determinants should also be identified to ameliorate inequality.

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Grupo étnico y el motivo del fracaso de la tecnología de reproducción asistida: análisis de los datos del registro de la Autoridad de Fertilización y Embriología Humana de 2017 a 2018.

Objetivo: Comprender cómo el riesgo de diferentes tipos de fallas de las Tecnologías de Reproducción Asistida (TRA) varía según el grupo étnico y explorar el papel de la mediación según la edad materna y la etiología sospechada.

Diseño: estudio observacional de 48,750 mujeres que realizaron tratamiento con TRA en el Reino Unido entre enero de 2017 y diciembre de 2018.

Ámbito: El registro nacional de TRA de la Autoridad de Embriología y Fertilización Humana del Reino Unido.

Paciente(s): Se incluyeron mujeres que comenzaron el primer ciclo de TRA con el fin de realizar una transferencia primaria de embriones frescos utilizando sus propios ovocitos.

Intervención(es): Grupo étnico materno.

Principal(es) medida(s) de resultado: Los tipos de fracaso de las TRA se modelaron en el grupo étnico materno utilizando la regresión de Poisson para producir riesgos relativos (RR) con intervalos de confianza del 95 %. Se estimaron los efectos indirectos potenciales de la edad materna y la etiología de la subfertilidad, y se generaron los RR con intervalos de confianza del 95%.

Resultado(s): Las mujeres negras tenían mayor riesgo de fracaso del tratamiento con respecto a los nacidos vivos que las mujeres blancas: cancelación del ciclo, RR de 2.15 (1.78–2.62); fertilización fallida, RR de 2.36 (1.90-2.93); congelación total involuntaria, RR de 1.71 (1.43–2.05); implantación fallida, RR de 1.23 (1.12-1.34); y pérdida del embarazo, RR de 1.38 (1.15-1.64). Las mujeres que eran asiáticas tenían un riesgo moderadamente mayor: RR de 1.31 (1.17 a 1.47), 1.60 (1.42 a 1.80), 1.25 (1.14 a 1.38), 1.11 (1.07 a 1.16) y 1.13 (1.03 a 1.23), en todos el mismo resultado, respectivamente. La desigualdad podría haberse reducido si las mujeres de todas las etnias hubieran iniciado el tratamiento a la misma edad.

Conclusión(es): Las mujeres negras tienen mayor riesgo de todos los tipos de fallas, y las mujeres asiáticas tienen un riesgo intermedio en comparación con las mujeres blancas. Algunos de los riesgos entre las mujeres que eran negras pueden estar mediados por la edad materna.