Blood type predicts live birth in the infertile population

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Abstract

Purpose To determine if blood type in infertile women relates to the likelihood for live birth (LB) following IVF, and to the etiology for infertility.

Methods Retrospective study of patients undergoing IVF at two academic centers in the northeast US. Relationships between blood type (A, B, AB, O) and patient characteristics, IVF cycle parameters and LB were assessed utilizing multi-variable logistic regression analyses.

Results In the studied population ($n=626$), women with type O were significantly more likely to have baseline FSH >10 IU/L after adjusting for age, BMI and race (OR 5.09, 95 % CI 1.4–18.7, $p=0.01$). Conversely, women with blood type A were significantly more likely to have ovulatory infertility compared to those with blood type O after adjusting for age and BMI (OR 3.2, 95 % CI 1.7–6.2). Blood type B was associated with increased likelihood of live birth (OR 1.9, 95 % CI 1.10–3.41, $p=0.03$) after adjusting for factors recognized to impact IVF outcome.

Conclusion Ovulatory infertility and baseline FSH >10 IU/L were more prevalent in women with blood type A and O respectively. However, those of blood type B had significantly higher

odds for LB compared to other blood types after adjusting for factors recognized to impact on IVF cycle outcome. While underlying mechanisms are unclear, for infertile women, patient's blood type is seemingly relevant for IVF cycle outcome.

Keywords Blood type · Infertility · Ovulatory dysfunction · Live birth · IVF

Introduction

In infertile populations, a relevance of blood type to reproductive wellbeing has been suggested. Binder et al. [1, 2] described an association between blood type A and an increased risk of early-onset ovarian hyperstimulation syndrome (OHSS) in infertile women undergoing in vitro fertilization (IVF). In an eastern Siberian population of women with gynecologic cancers, an increased risk of ovarian cancer was reported for premenopausal women of blood type A when compared with other blood types [3]. A study in the US found that infertile patients with endometriosis had a higher prevalence of blood type A compared to blood type O [4]. In a previous study of reproductive age infertile women, we had observed that women with blood type O were twice as likely to manifest evidence of diminished ovarian reserve (DOR) as defined by baseline early follicular phase FSH level of >10 IU/L, compared to those with blood types A or AB [5]. The presence of 'A' blood group antigen (i.e., blood types A or AB) was observed to relate with a reduced likelihood for DOR, an association that was independent of age. Despite these observed associations however, any potential underlying mechanisms remain unclear.

Based on our earlier findings [5], we hypothesized a higher oocyte yield, and possibly better clinical pregnancy rates following IVF in women of blood type A compared to those with

Capsule In an infertile population, we observed that blood type B was associated with increased likelihood of live birth.

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blood type O. This study builds upon our prior observation that if indeed blood type relates to the status of ovarian reserve in infertile women, then blood type may also relate to ovarian response to exogenous gonadotropins and to IVF cycle outcome.

Materials and methods

Study population constituted of infertile women undergoing IVF and embryo transfer at two clinical sites between 2007 and 2009. Notably, this study population is distinct from that reported previously [5]. Patient characteristics including age, body mass index (BMI), self-identified race and ethnicity, infertility diagnosis, blood type and Rh status, early follicular phase serum FSH (IU/L) and estradiol (E_2 , pg/mL) were collected. Cycle parameters such as cycle attempt (first versus repeat IVF), (type [intracytoplasmic Sperm Injection –ICSI, versus IVF), dose and duration of gonadotropin stimulation, E_2 on day of HCG trigger, number of eggs retrieved and number of embryos transferred were identified. FSH levels >10 IU/L was considered consistent with DOR in agreement with common practice guidelines at both study sites [5]. Live birth (LB) following fresh embryo transfer (ET) and FSH >10 IU/L were the primary and secondary outcomes of interest respectively whereas blood type constituted the independent variable of interest.

Statistical analysis

Data distribution was assessed. Associations between patient and IVF cycle variables with LB were determined using student's *T* test (for normally distributed variables including age, BMI, and baseline FSH) or Mann Whitney *U* test (for skewed data including dose of gonadotropins, duration of IVF stimulation, E_2 on day of hCG, endometrial thickness [mm] and number of embryos transferred, ET). Kruskal Wallis Rank test compared parameters across the four blood types (A, O, AB, B). Blood type A and AB were grouped as '*any blood type A*'; similarly, B and AB were grouped as '*any blood type B*' for additional analyses that utilized student's *T* test (for normally distributed data) or Mann Whitney *U* (for skewed data). Variables demonstrating statistical significance and those of biological relevance to outcomes of interest were included in a backward stepwise multivariable logistic regression analyses to identify predictors of LB (primary outcome) and for predictors of FSH >10 IU/L (secondary outcome). In the model building process, successive step wise elimination of non-significant variables resulted in identification of the most parsimonious model with the highest sensitivity. Associations are reported as odds ratio (OR) with a 95 % confidence interval (95 % CI) and *p* values <0.05 was taken as threshold for statistical significance; *p* values are reported up

to the second decimal place and for simplicity, $p < 0.01$ is taken to denote *p* values less than 0.01). Goodness of model fit reflected model sensitivity for specified outcomes of interest. STATA IC 11 (StataCorp, College Station, TX, USA) was used for statistical analyses.

Results

Information on LB was available for 617/626 (98.6 %) IVF cycles whereas information on self-identified race/ethnicity was available for only 173/617 (28 %). The distribution of individual blood types was consistent with reported prevalence within the US population [6] as follows: blood type O

Table 1 Patient and IVF cycle characteristics based on live birth (LB) outcome

Parameter	LB Yes (172)	LB No (445)	<i>P</i> -value
Age (yrs)	33.7 $\pm$ 4.5	35.6 $\pm$ 4.7	<0.01
BMI (kg/m ²)	26.3 $\pm$ 5.1	26.2 $\pm$ 5.7	0.40
Race (<i>n</i> =175)			0.94
White (123)	26 %	74 %	
Black (24)	22 %	78 %	
Asian (11)	27 %	73 %	
Hispanic (12)	27 %	73 %	
Other (5)	40 %	60 %	
Blood type			0.75
A	35 %	40 %	
B	19 %	13 %	
AB	6 %	5 %	
O	41 %	43 %	
Any Blood Type A (A or AB)	41 %	44 %	0.42
Any Blood Type B (B or AB)	24 %	17 %	0.05
Baseline FSH (IU/L)	6.4 $\pm$ 1.9	7.0 $\pm$ 2.4	<0.01
FSH >10 IU/L	3 %	11 %	<0.01
Infertility diagnosis			0.35
DOR	5 %	11 %	0.01
Ovulatory disturbance	53 %	46 %	0.04
IVF attempt # (1st versus repeat)	63 %	54 %	0.05
E_2 at HCG Trigger (pg/mL)	2381 $\pm$ 1105	2293 $\pm$ 1305	0.10
Days gonadotropin	10.2 $\pm$ 2.4	10.6 $\pm$ 2.0	0.26
Dose gonadotropin (IU)	2581 $\pm$ 1377	3131 $\pm$ 1549	<0.01
# Eggs retrieved	13.6 $\pm$ 7.1	12.3 $\pm$ 7.5	0.01
# Embryos transferred	2.5 $\pm$ 0.9	2.1 $\pm$ 1.2	<0.01
Blastocyst ET	23 %	13 %	<0.01
Cryopreservation achieved (Yes)	25 %	19 %	0.08
Endometrial thickness (mm)	7.1 $\pm$ 4.3	5.8 $\pm$ 4.8	<0.01

Continuous values presented as Mean $\pm$ SD

Categorical values presented as (%)

p-values that are significant at < 0.05 are bolded

42 %, type A 38.3 %, type B 14.9 % and type AB 4.8 %. The majority (90 %) of patient population was rhesus positive.

Primary question: is female blood type relevant to live birth following IVF-ET? Based on our earlier work [5] we had hypothesized a higher likelihood of LB following IVF-ET in women with blood type A and/or a lower likelihood of LB in those with blood type O.

Table 1 presents patient and IVF cycle data according to the primary outcome of interest, i.e., LB following ET. As is evident from presented data, women achieving LB were significantly younger, were significantly less likely to carry a known diagnosis of DOR, were more likely to have ovulatory dysfunction as a cause for infertility, had significantly better ovarian reserve (as reflected by baseline FSH), required significantly lower dose of gonadotropins during ovarian stimulation, yielded significantly higher number of oocytes at egg retrieval, and achieved a significantly higher endometrial thickness on the day of hCG trigger (Table 1). Notably, number of ET was significantly higher in the group achieving LB following IVF. Live birth following IVF-ET was unrelated to race/ethnicity.

On univariate analysis, the likelihood of LB following IVF-ET did not vary across the four blood types ($p=0.75$, Kruskal Wallis Rank Test, Table 1). While blood type A and O did not exhibit associations with LB as hypothesized, a higher likelihood for LB was noted in women of blood type B, or ‘any blood type B’ compared to other blood types (Table 2).

The two study sites were comparable in proportion of ICSI versus IVF cycles ($p=0.13$), blood type distribution ($p=0.60$), LB rate ($p=0.76$), but differed in day of ET ($p<0.001$), and number of ET ($p=0.08$). Study site was included as an adjustment variable in model building but was dropped out on step-wise backward regression modeling due to a lack of statistical significance to its association with LB. The final model included blood type, patient age, BMI, dose of gonadotropin,

endometrial thickness on the day of hCG, cryopreservation of surplus embryos, number and developmental stage of transferred embryo's, IVF attempt # (1st versus repeat) as covariates; women of blood type B were almost twice as likely to achieve LB following ET compared to those with blood types A or O (OR 1.9, 95 % CI 1.10–3.41, $p=0.03$), Table 2. The statistical model demonstrated 74 % sensitivity for the outcome LB.

Sensitivity analyses were conducted restricted to first IVF attempt ($n=265$) and up to 2 IVF cycles ($n=461$) to minimize any bias related to repetitive IVF attempts. The magnitude and directionality of association between blood type B and LB persisted on these sensitivity analyses (OR 2.2, 95 % CI 0.93–5.26 in analyses restricted to 1st IVF cycle and OR 2.17, 95 % CI 1.15–4.12 in analyses restricted to maximum of 2 IVF attempts).

Secondary question: does blood type relate to infertility diagnosis and ovarian reserve? Based on our earlier work [5] we anticipated a higher prevalence of blood type O amongst women with DOR.

Baseline FSH level did not vary by blood type ($p=0.37$, Kruskal Wallis Rank test, data not shown). However, the proportion of women with evidence of DOR based on baseline FSH > 10 IU/L was highest amongst those with blood type O (11 %) compared to blood types A (8 %), B (7 %) or AB (3 %), although the association was not of statistical significance on univariate analysis ($p=0.46$, Kruskal Wallis Rank test).

After adjusting for age, BMI and race, infertile women of blood type O were five times more likely to have baseline FSH > 10 IU/L compared to other blood types (OR 5.09, 95 % CI 1.4–18.7, $p=0.01$), Table 3. The statistical model demonstrated 83 % sensitivity for the outcome DOR based on baseline FSH > 10 IU/L.

The prevalence of ovulatory dysfunction diagnosis differed significantly by blood type (15 % in A, 9 % in B, 7 % in AB

Table 2 Independent predictors of live birth (LB) following IVF. Associations expressed as odds ratio (OR) and 95 % confidence interval (CI)

Variables	Unadjusted OR (95 % CI)	P-value	Adjusted OR (95 % CI)	P-value
Age (years)	0.9 (0.88–0.95)	<0.01	0.9 (0.82–0.92)	<0.0001
BMI (kg/m ²)	1.0 (0.97–1.04)	0.82	1.0 (0.95–1.03)	0.71
Blood type B vs. A	1.5 (0.95–2.45)	0.08	2.2 (1.15–4.11)	0.02
Blood type AB vs. A	1.3 (0.60–2.86)	0.5	2.0 (0.69–5.6)	0.21
Blood type O vs. A	0.9 (0.64–1.32)	0.7	1.2 (0.74–2.03)	0.43
Endometrial thickness (mm)	1.1 (1.02–1.10)	<0.01	1.0 (0.92–1.04)	0.46
Gonadotropin dose (IU)	1.0 (0.99–0.99)	<0.01	1.0 (0.99–1.00)	0.33
# Embryos transferred	1.3 (1.14–1.57)	<0.01	1.9 (1.46–2.42)	<0.01
Blastocyst transfer (Yes)	1.9 (1.22–3.01)	<0.01	2.1 (1.03–3.85)	0.04
First attempt at IVF vs. repeat	1.43 (0.99–2.0)	0.05	1.5 (0.91–2.36)	0.12

Model Sensitivity: 73 %

p-values that are significant at <0.05 are bolded

Table 3 Predictors of elevated baseline FSH (>10 IU/L). Associations are expressed as odds ratio (OR) and 95 % confidence interval (CI)

Variables	Unadjusted OR (95 % CI)	<i>P</i> -value	Adjusted OR ^a (95 % CI)	<i>P</i> -value
Age (years)	1.16 (1.08–1.24)	<0.01	1.23 (1.03–1.46)	0.02
BMI (kg/m ²)	0.91 (0.85–0.97)	<0.01	0.75 (0.60–0.94)	0.01
Blood type 'O' vs. other	1.43 (0.82–2.5)	0.21	5.09 (1.4–18.7)	0.01
White race vs. other	0.76 (0.24–2.4)	0.64	1.44 (0.40–5.3)	0.58

p-values that are significant at < 0.05 are bolded

^a Model sensitivity: 83 %. *N*=165 in the final model

and 6 % in blood type O, $p=0.004$, Kruskal Wallis Rank test); conversely, the blood type A was over-represented in women with ovulatory dysfunction (Fig. 1). In contrast to the above described association noted between blood type O and DOR, women of blood type A were three times more likely to carry a diagnosis of ovulatory dysfunction compared to blood type O (OR 3.2, 95 % CI 1.67–6.25, $p<0.001$) after adjusting for age and BMI, with a model sensitivity of 73 %.

Discussion

This study extends our prior observation relating blood type to ovarian biology. In a cross-sectional population of infertile women undergoing evaluation at two subspecialty fertility clinics, we had previously observed that blood type O was associated with a predisposition to DOR whereas women with blood type A were

less likely to manifest evidence of DOR as reflected by baseline FSH>10U/L [5]. Our current data, accrued in a population distinct from that we had previously reported on, reaffirms a prediction of blood type O to increased likelihood for FSH elevation, a phenomenon that is independent of age, BMI and race.

Diagnosis of ovulatory dysfunction was more commonly encountered in women with blood type A. Notably, ovulatory dysfunction is deemed a risk factor for ovarian hyperstimulation syndrome, an entity that also has been related to blood type A by others [1, 2]. We have now observed in two independent studies on women undergoing IVF that nature of infertility (specifically, diagnoses of DOR and ovulatory infertility) relates to blood type in infertile women [5]. Despite the association of blood type O with ovarian reserve however, ovarian response to exogenous gonadotropins is not influenced by blood type (data not shown).

Beyond associating blood type with ovarian reserve, we herein provide evidence that suggests a relevance of blood type for IVF cycle outcome, a phenomenon that has not been reported

Fig. 1 Increased prevalence of blood type A in infertile women with ovulatory dysfunction

previously. The presence of B antigen, either as blood type B or AB (any B blood group) doubled the likelihood for LB compared to blood types O or A (OR 1.9, 95 % CI 1.10–3.41, $p=0.03$). Women of blood type B were significantly more likely to achieve LB following IVF embryo transfer compared to those of blood types O and A after adjusting for parameters that are recognized to affect the likelihood of cycle success [7–12].

Despite prior research relating blood type to reproductive biology, mechanisms relating blood type with ovarian reserve or with LB remain unclear [2, 5, 13]. Blood type B along with type AB have the lowest prevalence in the US population (approximately 20 %) [6]. The A and B alleles of the ABO gene locus encode for glycosyltransferases that catalyze the transfer of galactose to the blood group H antigen, thereby conferring non blood type O (A, B, AB) phenotypes [5, 14, 15]. Several proteins crucial for follicle development and maturation, such as the FSH receptor and the LH receptor are heavily glycosylated proteins. In the absence of any mechanism to explain our findings, we reiterate our postulation that altered cell surface glycosylation may be of relevance in explaining the observed relationships between blood type O with ovarian reserve, blood type A with ovulation disturbance and blood type B with live birth following IVF; these conjectures merit further study through appropriately designed experiments.

Our prior and current findings stand in contrast with those recently reported by Timberlake et al. [13]. In a cross sectional study of 305 infertile women undergoing IVF at a single clinic in the southeastern US, the authors failed to observe any relationship between blood type and DOR. They reaffirmed a well-recognized phenomenon of protective implications of BMI for ovarian reserve (lower FSH levels in women of higher BMI) and suggested that our failure to include BMI in our study [5] could have accounted for results that could not be confirmed in their population. Presented data demonstrate that the observed associations between ovarian reserve and blood type are independent of BMI. Differences in the studied populations as well as differences in sample sizes on adjusted analysis (544 women at 2 sites [5] versus 232 women at a single site [13]) can be hypothesized to explain Timberlake et al.'s failure to substantiate what we had previously reported and now reaffirm.

Neither our studies, nor the work of Timberlake et al., drew associations of blood type with anti-mullerian hormone (AMH), a better marker of ovarian reserve than FSH [16]. The lack of observed associations between blood groups and IVF cycle parameters in response to exogenous gonadotropins suggests that altered gonadotropin signaling rather than size of residual egg pool (for which AMH is a better predictor than FSH) may underlie the observed link between blood group and FSH elevation.

A number of limitations are inherent to the study design (observational, non-randomized and retrospective). Information on race and ethnicity is missing for a significant proportion of the population and mechanisms that could explain the observed phenomenon are entirely unclear. Nonetheless, in a population

distinct from our last report, we confirm the previously observed association between blood type O and FSH elevation. Our finding relating blood type B to LB following IVF-ET is novel and mechanisms relating blood type to ovarian reserve and to the likelihood of LB remain to be elucidated.

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Conflict of interest None of the authors has any conflict of interest to declare.

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