

# Association of blood groups with ovarian reserve and outcome of in vitro fertilization treatment

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**BACKGROUND:** The association between ABO blood groups and ovarian reserve in infertile patients has been a point of controversy.

**OBJECTIVES:** The aim of this study was to assess the correlation of certain blood groups with ovarian reserve and response to treatment in patients undergoing infertility treatment.

**DESIGN:** Retrospective medical record review.

**SETTING:** Infertility clinic in the assisted reproductive technology (ART) unit at King Faisal Specialist Hospital and Research Center, Riyadh Saudi Arabia.

**PATIENTS AND METHODS:** All patients under 40 years of age who attended the infertility clinic at a tertiary care centre in 2010 and underwent in vitro fertilization (IVF) treatment in 2010 and 2011 were divided into groups according to blood type, and clinical parameters were compared.

**MAIN OUTCOME MEASURE(S):** The association between blood groups and ovarian reserve using day 3 luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels, and antral follicular count (AFC).

**RESULTS:** In 424 patients who underwent 566 IVF cycles, age, LH, FSH and AFC were similar among the different blood groups ( $P=.9$ ,  $.1$ ,  $.5$ , respectively). With controlled ovarian stimulation, no difference was observed among the four groups in menopausal gonadotrophin (hMG) dose or the duration of stimulation. The number of oocytes retrieved, fertilization rate, cleavage rate, and number of embryos transferred were similar. There was no difference in the cancellation rate or pregnancy rate among the groups.

**CONCLUSION:** There was no significant association between blood type and ovarian reserve or response during IVF treatment in our population.

**LIMITATIONS:** Anti-Mullerian hormone levels are best correlated with ovarian reserve testing. Unavailability of AMH levels. Retrospective design.

For the vast majority of women undergoing in vitro fertilization (IVF) treatment, controlled ovarian hyperstimulation (COH) is used and the outcome of the IVF treatment is affected by the ovarian response to COH and the number of the oocytes retrieved during the treatment cycle.<sup>1,2</sup> The treatment is usually tailored according to the ovarian reserve of the woman. Various factors, such as age, follicular stimulating hormone (FSH) level, antral follicular count (AFC) and anti-Mullerian hormone (AMH), are used to predict the ovarian reserve for couples undergoing fertility treatment.<sup>3</sup> The

results of ovarian reserve testing are an important part of patient counselling before starting treatment.

Since its introduction, the relationship to different pathologies to ABO blood groups has been of interest to researchers. Aird et al<sup>4</sup> reported the relationship of blood groups to gastric cancer. Later, Solish and Gershowitz<sup>5</sup> failed to find any correlation between infertility and blood groups. Recently, a predominance of blood group A was shown in patients with endometriosis.<sup>6</sup>

There has been interest in whether there could be an

association between blood groups and ovarian reserve recently. Blood group A might be associated with early onset of ovarian hyperstimulation syndrome.<sup>7,8</sup> Nejat et al<sup>9</sup> showed that blood type O was associated with diminished ovarian reserve and that the A blood group antigen appears to be protective of ovarian reserve. However, this finding was challenged by two different studies showing no correlation of blood groups to ovarian reserve.<sup>10,11</sup> On the contrary, Lin et al<sup>12</sup> showed that Chinese women with blood type O had less diminished ovarian reserve than women with blood types B and AB, who had more diminished ovarian reserve while blood type A was not associated with ovarian reserve. Pereira et al<sup>13</sup> studied the subgroups of patients with diminished ovarian reserve and found no difference in response to ovarian stimulation.

Since all ovarian reserve testing is performed to estimate the response of ovaries to exogenous gonadotrophin treatment, we analyzed the number of follicles grown and the number of oocytes obtained following COH to correlate to blood types as well as the final outcome of IVF, for an association with blood types. The aim of our study was to assess whether ovarian reserve and IVF treatment outcome are associated with certain blood groups.

## PATIENTS AND METHODS

All new patients who attended the infertility clinic in the ART unit at King Faisal Specialist Hospital and Research Center, Riyadh Saudi Arabia, in 2010 who had complete records were identified from our electronic database and their records were reviewed. Patients who were under 40 years old and had an IVF treatment cycle from 1 January 2010 to 31 December 2011 were included. The study was approved by institution Research Ethics Committee.

Data on the early follicular phase serum levels of FSH, luteinizing hormone (LH), antral follicle count (AFC) using the 3-dimensional -GE Voluson-I ultrasound scanner, dose of human menopausal gonadotrophin (hMG) used, days of stimulation, number of follicles grown beyond 10 mm, number of oocytes obtained, the cycle outcome, pregnancy rate, ovarian hyperstimulation syndrome (OHSS), blood type (A,B,AB and O) and the patient age were recorded in an Excel worksheet.

Patients had COH by either a long or short pituitary down regulation protocol. Human menopausal gonadotrophin (Menegon, Ferring, Germany) was used in all cases as the medication for stimulation. When there were at least three follicles  $\geq 18$  mm, 10000 IU human chorionic gonadotrophin (hCG, Choriomon, IBSA,

Switzerland) was administered to induce final follicular maturation. Oocyte retrieval was performed 36 hours following hCG injection. Fertilization was achieved by IVF or ICSI according to the indication. A maximum of two embryos were transferred under trans-abdominal ultrasound guidance with a full bladder on day 3. The patients started on a vaginal suppository (progesterone, Cyclogest 200 mg, Actavis, UK) three times per day on the day of embryo transfer for luteal phase support. Clinical pregnancy was confirmed by ultrasound for fetal cardiac activity three weeks after a positive hCG test.

Patients were divided into four groups according to blood type. All groups were compared for the various parameters. The association between blood groups and ovarian reserve using day 3 LH and FSH levels, and AFC were analyzed as the primary outcome measures. The association between blood group and the dose of gonadotrophins used, days of stimulation and number of oocytes obtained as well as the pregnancy outcomes served as the secondary outcome measures.

Statistical analysis was performed using S-plus 2000 (Mathsoft Inc., <http://goo.gl/oaeh6y>). The proportions of the different blood types were compared by the chi-squared test. For the other variables, ANOVA was used for parametric data, the sign- rank test for non-parametric data, and the chi-squared test for binomial data. *P* values  $<.05$  were considered statistically significant.

## RESULTS

The 424 patients included in the study underwent 566 IVF/intracytoplasmic sperm injection (ICSI) cycles during the study period. Group O blood type was the most common among our patient population (53.5%), while the AB blood type was seen only in 3.5% of the patients. Blood groups A and B were present 27.6 and 15.3% of the patients, respectively (**Table 1**). The patients' ages were similar among the different blood groups ( $P=.33$ , **Table 1**). Likewise, the proportions of patients older than 35 years were comparable among the blood groups.

Early follicular phase antral follicle count was similar among the different blood groups ( $P=.38$ ) and no difference was seen in the mean levels of LH and FSH among in the four groups (**Table 1**). The proportions of women whose FSH level was  $\leq 10$  mIU/mL or  $>10$  mIU/mL were not significantly different across the different blood groups ( $P=.1$ , **Table 1**). **Table 2** shows the characteristics of treatment cycles. During COH, no difference was observed among the four groups in hMG dose, duration of stimulation, and number of follicles  $>10$  mm on the day of hCG injection. Moreover, the

**Table 1.** Patient characteristics and blood group distribution (N=424).

| Blood group                         | O          | A           | B           | AB          | P value |
|-------------------------------------|------------|-------------|-------------|-------------|---------|
| Number of patients                  | 227        | 117         | 65          | 15          |         |
| Blood group (%)                     | 53.5       | 27.6        | 15.3        | 3.5         |         |
| Age (mean and SD)                   | 31.5 (6.0) | 31.5 (5.7)  | 31.0 (5.9)  | 28.8 (9.1)  | .33     |
| Age >35 (%)                         | 22.3       | 20.2        | 22.4        | 20.0        | .9      |
| Antral follicle count (mean and SD) | 13.6 (9.3) | 15.1 (10.2) | 14.9 (10.4) | 14.7 (10.3) | .5      |
| LH mIU/mL (mean and SD)             | 6.54 (4.5) | 6.63 (3.9)  | 6.69 (4.7)  | 6.87 (4.0)  | .9      |
| FSH mIU/mL (mean and SD)            | 6.99 (2.9) | 6.37 (2.5)  | 6.79 (3.1)  | 5.78 (2.0)  | .1      |
| Patients with FSH ≤10               | 209 (90%)  | 113 (95%)   | 65 (97%)    | 15 (100%)   | .1      |
| Patients with FSH >10               | 24 (10%)   | 6 (5%)      | 2 (3%)      | 0           | .1      |

hMG: human menopausal gonadotropin; IU: International unit; SD: Standard deviation; hCG: Human chorionic gonadotropin; OHSS: Ovarian hyper stimulation syndrome.

**Table 2.** Characteristics of IVF cycle and outcome by blood groups.

| Blood group                                      | O          | A          | B           | AB         | P value |
|--|------------|------------|-------------|------------|---------|
| Cycles   | 304        | 150        | 92          | 20         |         |
| Average dose of hMG (IU)                         | 3443       | 3630       | 3630        | 2978       | .4      |
| Days of stimulation (mean and SD)                | 11.2 (3.1) | 11.4 (2.9) | 11.5 (3.2)  | 11 (2.1)   | .87     |
| Cycles to oocyte retrieval                       | 285        | 113        | 84          | 18         |         |
| Cancelled during stimulation (%)                 | 18 (6)     | 6 (4)      | 6 (7)       | 1 (5)      | .17     |
| Follicles >10 mm on the day of hCG (mean and SD) | 13.9 (8.8) | 15.4 (8.7) | 15.0 (10.3) | 14.9 (7.2) | .38     |
| Oocytes retrieved (mean and SD)                  | 10.3 (6.5) | 11.1 (6.5) | 10.8 (7.0)  | 11.3 (5.8) | .68     |
| Immature oocyte (%)                              | 10.4       | 9          | 11.5        | 17         | .29     |
| Fertilization (%)                                | 66.2       | 63.9       | 70.1        | 56.1       | .35     |
| Cleavage (%)                                     | 95.2       | 93.3       | 93.9        | 94.8       | .60     |
| Embryos at 8-cell or more on day 3 (%)           | 40         | 42.8       | 43.7        | 50.5       | .73     |
| Good embryos (%)                                 | 53.6       | 51.6       | 53.9        | 48.5       | .8      |
| Poor embryos (%)                                 | 18.3       | 19.1       | 17.9        | 16.5       | .22     |
| Numbers of embryos transferred (mean and SD)     | 1.9 (0.6)  | 1.9 (0.3)  | 1.9 (0.3)   | 2 (0)      | .8      |
| Rate of OHSS (%)                                 | 3          | 4          | 5           | 0          | .71     |
| Pregnant   | 104        | 53         | 33          | 9          |         |
| Pregnancy rate/started cycle (%)                 | 34         | 35         | 36          | 45         | .8      |
| Pregnancy rate/patients (%)                      | 46%        | 45%        | 51%         | 60%        | .6      |

hMG: human menopausal gonadotropin; IU: International unit; SD: Standard deviation; hCG: Human chorionic gonadotropin; OHSS: Ovarian hyper stimulation syndrome.

number of oocytes retrieved was also similar among the different blood groups ( $P=.68$ , **Table 2**). Similarly, the embryological parameters in terms of percent immature oocytes, fertilization rate, cleavage rate, embryo quality, and number of embryos transferred were also comparable among the different blood groups (**Table 2**). The groups had a similar cancellation rate during stimulation and there was no significant difference in the rate of development of OHSS among the women in the four blood groups. The pregnancy rates were also similar among all groups (**Table 2**).

## DISCUSSION

The distribution of blood groups in this study was similar to that reported in a larger population study that included over 57 000 blood donors in Eastern Saudi Arabia.<sup>14</sup> The frequency of blood groups O, A, B and AB were 52%, 26%, 18% and 4%, respectively.<sup>14</sup> Therefore, these data further support the earlier information about the absence of any relationship between blood groups and infertility in different populations.<sup>5</sup>

Ovarian reserve is an important factor in the success of assisted reproductive technologies and there are still major difficulties in understanding the pathophysiology of ovarian reserve in reproductive medicine. There have been multiple studies trying to link certain genetic or environmental factors, which have been associated with the dynamics of the ovarian follicular pool, and ovarian response during COH.<sup>15-18</sup>

There has been recent interest on the effects of different blood groups on ovarian reserve and ovarian stimulation. Previous studies indicated that blood groups have differing implications for ovarian reserve. Specifically, that women with blood group O have been reported to have elevated baseline FSH levels compared with those with blood type A or AB,<sup>9</sup> and this elevation was independent of age. On the contrary, Chinese women with blood group O seem to have less diminished ovarian reserve.<sup>12</sup> In our study, we observed no relation of blood groups to the ovarian reserve. Early follicular phase FSH levels were similar among different blood groups. Moreover, the proportion of women having high FSH was also comparable. Similarly, de Mouzon et al<sup>10</sup> failed to show any relationship between blood groups and ovarian reserve by using AMH as a marker. AMH has been shown to be a better predictor of ovarian reserve than the classical markers including FSH.<sup>19</sup> We included AFC to assess the ovarian reserve in relation to blood groups. Apparently,

blood groups were not predictive of the ovarian reserve assessed by early follicular phase AFC in addition to FSH levels. Our data used to assess ovarian reserve is limited by the fact that we did not use AMH testing due to the unavailability of the test in our laboratory. However, we used the number of oocytes obtained as a real indicator of ovarian reserve since all testing for ovarian reserve estimates the response to ovarian stimulation and has failed to find any difference between blood groups. Similar results have also been reported in other studies recently.<sup>11,13,20</sup>

Contradictory results in one report<sup>9</sup> might stem from the study design and population differences. First of all, the information for cycle day when FSH measurement was performed was not available in Nejat et al<sup>9</sup> study. Estradiol values were used to estimate the early follicular phase while FSH measurements were strictly performed on cycle day 3 in our study. At the same time, population differences could be a factor since opposite results were obtained in Chinese women.<sup>12</sup> Such population differences were also observed in the distribution of endometriosis among different blood groups. A higher incidence of endometriosis in blood group A was demonstrated in US and Korean centers, respectively.<sup>6,21</sup> Demir et al<sup>22</sup> failed to show any association in between blood groups and endometriosis in Turkish population.

The results of our study and Bellver et al<sup>23</sup> were not consistent with earlier reports of an association between blood groups and OHSS.<sup>7,8</sup> The discrepancy could be explained by the fact that the sample size of patients having OHSS was very small in our study, especially when it was split into the four blood groups. Any correlation between OHSS and blood groups needs to be further evaluated in a larger study.

We have also compared the characteristics and outcome of treatment cycles to blood groups. There was no significant difference in the doses of gonadotrophins used, days of stimulations, the number of the oocytes retrieved and fertilized, embryo quality and pregnancy rates among the four groups. Spitzer et al<sup>20</sup> also failed to show any association between the cycle outcome measures and blood groups. Another limitation of our study was the retrospective design. In conclusion, we found no association between blood type and ovarian reserve, ovarian response or IVF treatment outcome.

## Conflict of interest

*The authors have no conflicts of interest.*

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