Impact of Living in Different Altitudes on Intracytoplasmic Sperm Injection (ICSI) Outcomes for Infertile Couples in Southwestern Region of Saudi Arabia, a Retrospective Study

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Abstract

Objective: The aim of this study was to determine the effect of different altitudes in the Southwestern region of Saudi Arabia on ICSI outcomes, fertilization rate, embryo quality, pregnancy rate, and miscarriage rates for infertile couples.

Materials and Methods: This is a retrospective study on 551 infertile couples carried out in the *Assisted Reproductive Technology* unit at the Maternity and Children Hospital in Abha, Saudi Arabia between 2018 and 2019 to compare ICSI outcomes in different altitudes. Low altitude (205 patients), mild altitude (86 patients) and high altitude (260 patients). Main result measurements: fertilization rates, embryo quality, clinical pregnancy and miscarriage rates at different altitudes.

Results: The data showed that there were no significant differences ($P>0.67$) in fertilization rates and the number of good-quality embryos between different altitudes. Importantly, clinical pregnancy rates were similar between groups and there was no significant difference in the miscarriage rates between high, mild and low altitudes.

Conclusions: This study demonstrates that there is now increased risk of miscarriage or low pregnancy rates with different altitudes in Southwestern region of Saudi Arabia. This suggests that altitude changes has no obvious risk on pregnancy rate and pregnancy outcome.

Key Words: ICSI; high altitudes; pregnancy rate

List of Abbreviations:

Assisted Reproductive technology (ART).

Intra-Cytoplasmic Sperm Injection (ICSI).

In vitro fertilization (IVF).

Oxidative stress (OS).

Reactive oxygenated species (ROS).

Reactive oxygen and nitrogen species (RONS).

1. Introduction

High altitude is defined as an elevation of more than 2500 m, which is mainly characterized by a lower partial pressure of O₂ (Po₂) relative to sea level at the same latitudes [1]. A high-altitude environment exerts a potential challenge to humans who are living or traveling at high altitude hypoxic regions [2]. Notably, pregnancy at high altitude is a significant burden for both the mother and fetus [2].

15% of couples around the world suffer from infertility, 56% of whom seek medical assistance to conceive. Intra-Cytoplasmic Sperm Injection [ICSI] was introduced in 1992[3]. Although it was meant to be for couples with male factor infertility at first, it is now suggested for couples with non-male factor infertility largely 100% in some parts of the world [4].

ICSI has higher fertilization rates than In vitro Fertilization [IVF] as it may avoid some of the possible fertilization barriers.

There are numerous factors that influence the success of ICSI. One such factor is oxidative stress [OS], which is the imbalance between reactive oxygenated species (ROS) and antioxidants in the body. Oxidative stress plays a role in multiple physiological processes of the female reproduction, from oocyte maturation to fertilization, embryo development, pregnancy, and parturition. It is a modulator of germ cell and stromal cell physiology. The ROS released from NADPH oxidase is also critical for vascular endothelial growth factor [VEGF] signaling in vitro, and for the angiogenesis in vivo [5]. This is important for normal key processes as follicular development, endometrial growth, embryo development, and growth of placental vessels [5].

However, plethora of literature [5,6] have been reported that OS play a role in infertility and has negative effect on the outcomes of assisted reproductive techniques either IVF or ICSI. The generation of ROS and consequent OS is inevitable in vitro setting particularly with the absence of natural antioxidants present in the tubal fluid. For example, using the embryo culture media's in vitro procedures during IVF or ICSI has potential to generate ROS, and other environmental factors such as the difference in P_{O_2} , all contribute to expose the embryo to large amounts of OS. Supraphysiological levels of ROS and OS can affect the gametes, fertilization rates and embryo quality [6]. It damages the gametes by lipid peroxidation, DNA fragmentation and apoptosis of the spermatozoa, and damaging the meiotic spindle of the oocyte which consequently reducing gametes quality, oocyte penetration and embryo implantation leading to increase early pregnancy loss [6].

Interestingly, decreased oxygen pressure in high altitude exposure results in OS and an increase in the generation of reactive oxygen and nitrogen species [RONS], which is associated with oxidative damage to lipids, proteins, and DNA. This effect is possibly not countered by antioxidant as living in high altitude appear to decrease the effectiveness and activity of the antioxidant enzyme system [7, 8]. OS and RONS are suggested to be a causative factor of mountain sickness. Therefore, oxidative damage to lipids, proteins, and DNA during high altitude exposure could also possibly reduce the quality of gametes, embryo, and consequently reproductive outcomes of ART.

It is reported that hypoxia in high altitudes can affect the development and function of corpus luteum in sheep, leading to decreased fertility. The corpus luteum in sheep exposed to high altitude hypobaric hypoxia for short or long time periods were smaller in size than the corpus luteum of ewes at a low altitude hypoxia [9]. The effects of high-altitude hypobaric hypoxia on sheep ovarian structure are possibly linked to the inadequate development and maturation of preovulatory follicles [10], and/or inadequate LH secretion, which is necessary for the final maturation of the preovulatory follicles, and subsequently, adequate development of the corpus luteum [11, 12, 13, 14].

Epidemiological and animal studies have shown that exposure to high altitude hypobaric hypoxia increases the incidence of pregnancy complications such as intrauterine growth restriction (IUGR), aberrant organ development, and neuro behavior disorder in neonates, neonatal morbidity [15, 16], and affect the development and function of the corpus luteum [9].

Thus, the previous studies suggest that living in high altitude with decreased oxygen pressure have drawback effects on reproduction, embryo development, and pregnancy, however, it is not yet known whether high altitude exposure would affect reproductive outcomes following ART (IVF or ICSI), where in vitro procedures have further potential to generate more ROS and OS. Further studies are needed to examine this [7, 8]. The aim of this study was to determine the effect of altitude change on ICSI outcomes (fertilization rate, embryo quality,

pregnancy rate, and miscarriage rates) for infertile couples living in different areas in Southern region of Saudi Arabia. In other words, does low oxygen tension in high altitude negatively affect ICSI outcomes compared to low altitude? To the best of our knowledge, this has never been assessed in previous studies.

2. Materials and Methods

ICSI outcomes, fertilization rate, embryo quality, pregnancy rate, miscarriage and live birth rate) were compared in infertile couples whether due to male factor, female factor or unexplained. This was done by retrospectively reviewing a chart of 551 ICSI cycles performed the Assisted Reproductive Technology unit at the Maternity and Children Hospital in Abha, Saudi Arabia between 2018 and 2019. The approval for this study was granted by the research ethical committee of the Maternity and Children Hospital, Abha, Saudi Arabia (REC # 2018-02-02).

The hospital system determined the medical record numbers of patients who attended the infertility clinic and underwent full assessment. The patient's data was extracted from their medical files. It included their history, female age, antral follicle counts (AFC), and laboratory results, such as the assessment of follicle-stimulating hormone (FSH) (Blood Hormones Assay being run in Cobas 6000, Roche Diagnostics, North America) and the causes of infertility (anovulation, tubal factor, unexplained, male factor and endometriosis).

Infertile couples were divided into 3 groups according to their living environments/level of altitudes: Low altitude (205 patients), mild altitude (86 patients) and high altitude (260 patients).

2.1 Inclusion criteria

The inclusion criteria in this study was constituted of couples suffering from primary or secondary infertility for at least one year, couples with unexplained, female, or male factor infertility, couples who have undergone ICSI, females aged between 18 and 40, and exclusion criteria females over 40 years of age.

2.2 Stimulation protocol and embryology procedures

The 3rd. day of the menstrual cycle is the standard time in our clinic to start ovarian stimulation. The patient's age, FSH levels of day 2 and 3, and Antral Follicle Count (AFC) determine the dose of gonadotropin. The response to stimulation is observed through the follicles growth and estradiol (E2) level. When at least 3 or more follicles are 17mm in size, hCG is administered, 34-36 hours after which ovum pick is performed. As for ICSI, oocyte maturation was examined by removing the cumulus 2 hours after retrieving the oocyte. The husband's spermatozoa were injected in metaphase II (MII) oocytes, at least 1 h post cumulus removal. Oocytes that failed to mature were discarded. Fertilization was assessed 16-18 h after insemination.

2.3 Fertilization rates

At the observation of two pronuclei (2PN) and two distinct or fragmented polar bodies, the oocytes were considered normally fertilized. The number of oocytes normally fertilized was divided by the number of injected oocytes to calculate the fertilization rate in ICSI. The data only included cases in which four mature eggs were injected for ICSI. This was done to reduce the influence of minimal egg numbers.

2.4 Embryo quality

Presence of four cells on day 2 and/or seven or eight cells on day 3, fragmentations less than 20%, and absence of morphological abnormalities, are the factors that regarded the cleaved embryo's as those of good quality. The usual practice in our clinic is to transfer the embryos on luteal day 3 according to age. Patients under the age of 35 receive two embryos and those above the age of 35 receive three. In the event that the

patient's embryos are not of optimum number or quality, their transfer on luteal day 2 is considered. The number of good embryos were divided by the number of cleaved embryos to assess the proportion of good embryos. The study only included cases with four cleaved embryos. This was done to reduce the influence of minimal embryo numbers.

2.5 Clinical pregnancy

Clinical pregnancy was determined by the presence of gestational sac and/or fetal heart beat on ultrasound at week 6 or 7 of pregnancy. To calculate the proportion of clinical pregnancy, the number of clinical pregnancies was divided by the total number of patients who took pregnancy test regardless of its result.

2.6 Miscarriage

Miscarriage was defined as an abortion before the 24th week of gestation. The proportion of miscarriage was calculated by the number of abortion cases was divided by the total number of patients with positive pregnancy results.

2.7. Statistical analysis

Normality of data was assessed according to the Kolmogorov-Smirnov test. Results were expressed as the mean $\pm$ standard deviation (SD), median and range for demographic data of sub-fertile couples undergoing ICSI. Statistical comparisons were made using the analysis of variance (ANOVA) if the data were either originally normally distributed or normalized after transformation by linear regression. However, some data were not normalized by transformation. The statistical comparisons for these data were examined by nonparametric Kruskal-Wallis one-way analysis of variance on ranks. The differences in proportions of clinical pregnancy and miscarriage rates between the groups (Low, mild, and high

altitude) were examined using a Chi-squared test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the Sigma plot 14 statistical package from Systat Software Inc. in Chicago, Illinois.

3. Results

551 infertile couples undergoing ICSI were divided into 3 groups according to their living environments/level of altitudes: low altitude (205 patients), mild altitude (86 patients) and high altitude (260 patients). The 3 groups were compared in terms of female age, infertility duration, and number of embryos transferred. No significant differences were found between the groups (Table 1).

There was no significant difference in fertilization rates (figure 1) or embryo quality (figure 2) between the low, mild and high-altitude groups.

The clinical pregnancy and miscarriage rates were not significantly different between various altitude levels. Clinical pregnancy rate was 22% in high altitude, but this proportion was not significantly different from those in low altitude 26% ($\chi^2 = 0.597$, $P = 0.44$) and mild altitude 28% ($\chi^2 = 0.723$, $P = 0.40$) (figure 3). The proportion of miscarriage was 45% in low altitude, 35% in mild altitude, and 43% in high altitude, which were not significantly different between groups.

Conclusion:

There is no difference in ICSI outcome regarding different altitudes. Further studies are required to support our research work.

Groups		Age	Infertility duration	No. of ET
Low Altitude (n= 205)	Mean $\pm$ SD	33.6 $\pm$ 6.3	5.9 $\pm$ 4	3.1 $\pm$ 1.1
	Median	33	5	4
	25%, 75%	29, 39	3, 8	2, 4
Mild Altitude (n= 86)	Mean $\pm$ SD	34.7 $\pm$ 6.7	6.1 $\pm$ 3.8	3.2 $\pm$ 1.1
	Median	35	6	4
	25%, 75%	31, 40	3, 8	2, 4
High Altitude (n= 260)	Mean $\pm$ SD	34.3 $\pm$ 6.3	6.1 $\pm$ 3.6	3.1 $\pm$ 1.3
	Median	35	5	4
	25%, 75%	30, 38.7	4, 8	2, 4

Table 1: Demographic characteristics of infertile groups undergoing ICSI. Infertile couples were divided into 3 groups according to their living environments/level of altitudes: Low altitude, mild altitude, and high altitude.

Figure 1: Comparison of fertilization rates (FR) in three groups of infertile patients (low altitude (red), mild altitude (green), high altitude (pink)). Box and whisker plots illustrating the data distribution for FR in the three groups of infertile patients. The boxes represent the interquartile range and lines within them are the medians. The number in brackets is the sample size in each group of patients. There were no significant differences between groups. Significance was considered as $P < 0.05$ assessed by one-way ANOVA and non-parametric ANOVA on ranks Kruskal–Wallis test.

Figure 2: Comparison of good embryos rates in three groups of infertile patients (low altitude (red), mild altitude (green), high altitude (pink)). Box and whisker plots illustrating the data distribution for good embryos rates in the three groups of infertile patients. The boxes represent the interquartile range and lines within them are the medians. The number in brackets is the sample size in each group of patients. There were no significant differences between groups. Significance was considered as $P < 0.05$ assessed by one-way ANOVA and non-parametric ANOVA on ranks Kruskal–Wallis test.

Figure 3: Comparison between the proportion of clinical pregnancy in three groups of infertile patients (low altitude (red), mild altitude (green), high altitude (pink)). No significant differences in % clinical pregnancy between groups. Significance was considered as $P < 0.05$ assessed by a Chi-squared test.

Discussion

Epidemiological and animal studies have shown that exposure to high altitude hypobaric hypoxia increases the incidence of pregnancy complications such as intrauterine growth restriction [IUGR], aberrant organ development, and neuro behavior disorder in neonates, neonatal morbidity [15, 16]. A Study by Gilbert RD et al has been reported that high altitude exposure during pregnancy affects fetal cardiovascular programming. The changes of cardiovascular system are variables and depends on the person's predisposition, oxygen level, and the exposed time at high altitude [2, 17]. In acute short-term exposure to high altitude hypoxia, the fetal cardiovascular system initial response is characterized by increasing systemic vascular resistance, blood pressure, heart rate, and cardiac output, which are mainly regulated by higher sympathetic activity and hyperventilation [18]. In response to long-term high altitude hypoxia exposure decreased protein expression in the fetus, suggesting that the gene repression may be one of the common mechanisms of underlying prenatal insults-mediated cardiac ischemic injury. Although the molecular mechanisms underlying high altitude hypoxia mediated cardiac gene expression remain unclear [19, 20].

Moreover, the growth of corpus luteum was altered in sheep exposed to high altitude and was confirmed by analysis of the expression key factors involved in the growth and vascularization [9]. Hypoxia in high altitude negatively affect the expression of both IGF-I and IGF-II, which are considered essential for early development and function of corpus luteum [21, 22]. A close relationship among vascularization, blood flow, and

progesterone production and secretion has been reported in the bovine corpus luteum [23]. It has been reported that sheep pregnancy in high altitude causes intrauterine growth retardation and low concentration of secreted progesterone. Interestingly, these effect were prevented by the supplementation of antioxidant vitamins [C and E] as the levels of plasma progesterone and the newborn lamb weights were increased, suggesting that these effects involve hypoxia and OS [24].

Women exposed to acute hypobaric hypoxia showed higher concentrations of plasma progesterone during the luteal phase than controls under normoxia [25]. Additionally native non-pregnant women living at a high altitude had greater levels of progesterone during the luteal phase of the menstrual cycle comparing with women residing at sea level [26]. A possible cause is an increased vascularization of the corpus luteum, which accordingly, an increased the progesterone secretion [27]; however, as discussed previously, this explanation does not fully fit with the observations in high altitude naive animals. Feasibly, the differences results from the variations between species and in the metabolism of progesterone rather than in secretion [28].

It has been reported that the hypoxia in high altitude triggers the activation of [RONS] generating systems, while reducing the activity of the antioxidant enzyme system [7, 8]. The consequent oxidative stress causes DNA fragmentation. It is known that DNA fragmentation negatively impacts the outcomes of assisted reproduction treatments such as impaired embryo development and pregnancy [29].

Thus, the previous studies suggest that living in high altitude with decreased oxygen pressure have drawback effects on reproduction, embryo development, and pregnancy. However, in our study there was no significant differences amongst the low, mild, and high-altitude groups in terms of fertilization rates, embryo quality, and pregnancy or miscarriage rates following ICSI. The outcomes of this study highlight the impact of living in different altitude environments on ICSI reproductive outcomes, and suggesting high altitude has no obvious risk on pregnancy. Further studies are required to examine this, which could improve future interventions in patients' care and treatments.

Conclusion:

There is no difference in ICSI outcome regarding different altitudes. Further studies are required to support our research work.

List of Abbreviations:

Assisted Reproductive technology (ART).

Intra-Cytoplasmic Sperm Injection (ICSI).

In vitro fertilization (IVF).

Oxidative stress (OS).

Reactive oxygenated species (ROS).

Reactive oxygen and nitrogen species (RONS).

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