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The Impact of Seasonal Variation on Clinical Pregnancy and Live Birth Rates in Assisted Reproductive Technology: A Retrospective Cohort Study in Hainan

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Abstract: *Objective:* To investigate the influence of season on live birth and clinical pregnancy rates, as well as assisted reproductive technology (ART) outcomes, in the Hainan region. *Methods:* Patients were categorized into four groups based on the dates of artificial insemination and transplantation: spring, summer, autumn, or winter. The main outcome measures were clinical pregnancy rates and live birth rates. Secondary outcomes included body mass index (BMI), oocyte number, two pronuclei (2PN) cleavage rate, total gonadotropin (Gn) dosage and days, age, 2PN fertilization rate, sperm concentration, sperm PR rate, anti-Müllerian hormone (AMH), and endometrial thickness. Outpatient semen quality indicators included sperm PR rate, total sperm count, sperm concentration, and total sperm motility. *Results:* This retrospective cohort study analyzed 2,016 artificial insemination cycles and 1,783 ovarian retrieval cycles from January 2017 to October 2022, and assessed the semen quality of 6,651 outpatients from May 2017 to October 2022. In artificial insemination cycles, sperm PR rate and clinical pregnancy rate were highest in winter, with a statistically significant difference between groups ($P < 0.05$). Clinical pregnancy rate was influenced by both age and sperm PR rate ($P < 0.05$). In ovarian retrieval cycles, the winter group had significantly higher clinical pregnancy, 2PN fertilization, and 2PN cleavage rates than the other groups. The autumn group had higher live birth rates, though not significantly different. Additionally, winter months showed higher total sperm concentration and total sperm number compared to other seasons. *Conclusion:* Seasonality affected clinical pregnancy and live birth rates in artificial insemination cycles but not in ovarian retrieval cycles in the Hainan region. These findings suggest that while there is no need to choose a specific season for ovarian retrieval cycles, artificial insemination in winter may be preferable for patients.

Keywords: Endocrinology; Assisted reproductive technology; Seasonality; Pregnancy rate; Artificial insemination

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1. Introduction

Research on the seasonal distribution of natural human pregnancy and childbirth rates has shown that in tropical regions, summer season fertility decreases due to reduced sperm quality, leading to lower pregnancy and birth rates [1,2]. In contrast, in regions with strong seasonal variations in sunlight, fertility rates peak in summer, resulting in the highest birth rates in spring [3]. Seasonal factors affecting fertility have long been recognized, with recent studies revealing that variations in temperature and light impact women's reproductive cycles and egg quality. For instance, the probability of live births from frozen embryo transfers for patients undergoing egg retrieval in summer increases by 30% compared to autumn [4]. Factors such as female age, the number of high-quality embryos, and endometrial receptivity significantly influence embryo implantation [5].

Past analyses of these factors have been limited by clinical and laboratory internal data. Recently, researchers have shown increased interest in the influence of environmental attributes on the effectiveness of assisted reproductive technology (ART) in humans. Previous studies found positive correlations between relative humidity and two pronuclei (2PN) incidence, with temperature and atmospheric pressure significantly associated with high-quality embryo rates [6].

Studies on whether seasonal changes affect the clinical pregnancy outcomes of *in vitro* fertilization and embryo transfer (IVF-ET) patients have yielded varied conclusions, influenced by geographical location, climatic environment, temperature, and daylight duration differences. While some studies suggest diminished autumn fertilization and implantation rates and increased spring pregnancy rates, others report a substantial rise in pregnancies during winter ART [1,7]. However, some researchers have found no substantial seasonal variations in live birth rates, clinical pregnancies, or fertilization after ART [8,9]. These inconsistencies may be due to differences in research populations, ART treatment approaches, ethnic groups, and regional variations in season types and durations [10-12].

There are no published studies on the influence of seasonal variation on assisted reproductive outcomes in Hainan Province. This study aims to investigate whether different seasons significantly affect the treatment outcomes of artificial insemination (AI) and to understand the possible reasons for this effect. By analyzing outcome data from different seasons and examining whether seasonal changes are related to patient laboratory results and clinical pregnancy outcomes, we can better understand how seasonal factors in Hainan affect the treatment outcomes of infertile patients and provide important references for clinical practice.

2. Materials and methods

2.1. Population and study design

A retrospective cohort study was conducted at the Hainan Women and Children Medical Center's Reproductive Center between January 2017 and October 2022. Patients were sorted into four groups based on the date of transplantation and artificial insemination: spring (March to May), summer (June to August), autumn (September to November), and winter (December to February). Semen analysis was performed using routine examination and analytical methods, following the WHO Laboratory Manual (5th edition) standards after complete liquefaction [13]. Embryo evaluation adhered to the Istanbul consensus standards [13].

Patients undergoing IVF cycles were grouped according to the oocyte retrieval date. Correlation analyses were conducted to compare the clinical pregnancy rate, 2PN fertilization rate, and live birth rate among the four groups. Patients undergoing artificial insemination cycles were also grouped by the artificial insemination date, and correlation analyses were performed to compare sperm viability, clinical pregnancy rate, and live birth rate among the groups.

2.2. Assisted reproductive technology protocol

The institutional ART protocol was followed. We utilized 100–300 IU of recombinant follicle-stimulating hormone (Merck Serono, Inc.) in an agonist (long, ultralong, short) or antagonist protocol. Recombinant hCG (250 µg; Merck Serono, Inc.) was administered subcutaneously to induce ovulation when three follicles reached a diameter of 17 mm. Transvaginal oocyte retrieval was performed 35 to 36 hours after the trigger under conscious sedation.

Semen processing: On the day of oocyte retrieval, a small ejaculate sample or an additional specimen was acquired through percutaneous epididymal sperm aspiration or testicular sperm aspiration and processed using density gradient centrifugation (Gradient, Bloomington, USA). Processed samples were incubated in a carbon dioxide incubator for 1 to 2 hours.

Oocyte collection and fertilization: Oocytes were collected, identified, graded, and incubated in an oil-covered culture medium. After 3–4 hours of incubation at 37°C, 6% CO_2, 5% O_2, and 89% N_2, mature oocytes were used for *in vitro* fertilization or intracytoplasmic sperm injection (ICSI). Fertilization was confirmed 16–18 hours after ICSI or 18–20 hours after *in vitro* fertilization.

Clinical and laboratory-related data, such as age, anti-Müllerian hormone (AMH) concentration, body mass index (BMI), number of oocytes, sperm concentration, sperm percentage at relapse (PR%), and 2PN rate, were obtained from the department's electronic database. Live birth data were collected through telephone interviews.

2.3. Observational indicators

The day after the oocytes were retrieved, the status of fertilization was determined, and embryos that 2PN were regarded as normal zygotes. These embryos were subsequently transferred to a cleavage medium for continued culture. The subsequent observation included monitoring embryo division and development. Depending on the patient's circumstances, the endometrial condition, as well as embryo quality, a fresh embryo transfer was carried out. Live birth and clinical pregnancy were the primary results, while miscarriage was considered a secondary outcome.

2.4. Statistical analysis

The study employed multiple logistic regression models to account for possible confounding variables, including total Gonadotropin (Gn) dose, BMI, female age, AMH level, total Human Chorionic Gonadotropin (HCG) dose, oocyte count, baseline E2, baseline FSH, baseline LH, baseline AMH, 2PN fertilization rate, normal cleavage rate, sperm concentration, and sperm vitality. When the variances were homogeneous, multiple groups' continuous variables were compared via a one-way Analysis of Variance (ANOVA). The statistical analysis was performed via SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), with the significance level established at $P < 0.05$.

3. Results

Overall, 2,016 artificial insemination cycles and 1,783 ovarian retrieval cycles from January 2017 to October 2022 were analyzed. Depending on the timing of artificial insemination and transplantation, patients were categorized into four groups: (1) spring (March to May), (2) summer (June to August), (3) autumn (September to November), and (4) winter (December to February).

3.1. Artificial insemination outcomes

Among artificial insemination patients, the winter group had the highest sperm PR rate and clinical pregnancy rate, with significant differences observed between the groups (*P* < 0.05). There were no statistically significant differences between the other groups (*P* > 0.05; see **Table 1**). However, the summer group had the highest live birth rate, and the winter group had the highest sperm concentration.

Table 1. Patients' general characteristics and pregnancy outcomes by season

Item	Spring	Summer	Autumn	Winter	*P*
Cycle number	475	580	526	435	
BMI (kg/m^2)	23.02 ± 17.49	23.25 ± 17.7	22.30 ± 11.43	22.87 ± 15.53	0.900
Seprm concentration ($\times 10^6$/mL)	57.60 ± 36.77	55.95 ± 34.97	56.87 ± 34.52	60.05 ± 38.27	0.438
Sperm PR %	49.97 ± 17.10	50.41 ± 17.47	52.05 ± 17.68	52.32 ± 18.08	0.032
Clinical pregnancy rate (%)	19.37 (92/475)	17.41 (101/580)	15.97 (84/526)	22.53 (98/435)	0.000
Live birth rate (%)	82.61 (76/92)	84.16 (85/101)	79.76 (67/84)	76.53 (75/98)	0.122
Age	31.42 ± 4.53	31.39 ± 4.36	32.04 ± 4.57	31.56 ± 4.63	0.000

Displayed as the mean ± standard deviation, while *P* < 0.05 indicated statistically significant differences

Multivariate logistic regression (MLR) analysis was conducted on pregnancy outcome indicators (age and sperm PR rate), and significant indicators were included. Compared to the winter season, the clinical pregnancy rates were 0.834, 0.718, and 0.658 in the spring, summer, and autumn groups, respectively. There was a significant correlation between the clinical pregnancy rate (*P* < 0.000), age (*P* < 0.000), and sperm percentage (*P* < 0.032) (**Table 2** and **Figure 1**).

Table 2. Assessment of pregnancy outcomes via logistic regression

Season	Clinical pregnancy		Live birth	
	aOR (95% CI)	***P***	**aOR (95% CI)**	***P***
Winter	Reference	-	Reference	-
Spring	0.834 (0.60–1.15)	0.267	1.35 (0.66–2.78)	0.411
Summer	0.718 (0.52–0.98)	0.038	1.63 (0.77–3.44)	0.197
Autumn	0.658 (0.47–0.91)	0.012	1.07 (0.52–2.20)	0.857

Abbreviation: aOR, adjusted odds ratio

Figure 1. Artificial insemination clinical pregnancy rate (%) by seasons

3.2. Ovarian retrieval outcomes

Among the ovarian retrieval cycles, the winter group exhibited a significantly higher rate of clinical pregnancy, 2PN fertilization, and 2PN cleavage compared to the other groups. The autumn group had a higher live birth rate compared to the other three groups. When age (*P* < 0.000) and endometrial thickness (*P* < 0.023) were assessed using MLR, statistically insignificant differences were found (*P* > 0.05). Additionally, during the ovarian retrieval cycle, the clinical pregnancy rate (*P* < 0.05; see **Table 3**) was impacted by the sperm PR rate (*P* < 0.004).

Table 3. Patient clinical characteristics and pregnancy outcomes

Item	Spring	Summer	Autumn	Winter	*P*
Cycle number	436	567	435	345	
Total dosage of Gn used (d)	9.94 ± 1.96	10.07 ± 1.80	10.16 ± 2.04	9.98 ± 1.71	0.581
Length of Gn used	1,909.71 ± 669.21	1,895.29 ± 671.61	1,904.54 ± 710.31	1,897.58 ± 573.43	0.541
2PN fertilization rate (%)	67.92 ± 19.88	69.84 ± 18.88	69.62 ± 18.79	70.26 ± 17.12	0.382
2PN cleavage rate (%)	96.97 ± 6.61	97.20 ± 8.24	97.75 ± 7.20	98.11 ± 5.40	0.717
AMH	3.77 ± 2.87	3.74 ± 2.92	3.82 ± 3.4	3.46 ± 2.78	0.475
Age (year)	33.46 ± 4.91	32.76 ± 4.61	33.18 ± 4.31	32.58 ± 3.97	0.000
AFC (n)	12.30 ± 5.65	12.71 ± 5.70	12.36 ± 5.50	12.08 ± 5.30	0.255
Sperm concentration ($\times 10^6$/mL)	66.01 ± 28.83	57.98 ± 36.20	61.25 ± 36.64	63.14 ± 38.23	0.669
Sperm PR (%)	53.72 ± 14.42	48.62 ± 18.14	49.94 ± 18.08	52.50 ± 19.10	0.004
Clinical pregnancy rate (%)	60.1 (262/436)	60.5 (343/567)	60.7 (264/215)	62.3 (215/345)	0.053
Live birth rate (%)	79.4 (208/262)	82.2 (282/343)	84 (221/343)	83.3 (179/215)	0.561
Endometrial thickness	11.11 ± 2.30	11.21 ± 2.19	11.34 ± 2.30	11.41 ± 2.22	0.023

Displayed as the mean ± standard deviation, while $P < 0.05$ indicated statistically significant differences

3.3. Outpatient semen quality outcomes

During winter, sperm concentration, total sperm count ($P < 0.005$), total sperm number ($P < 0.000$), total sperm motility ($P < 0.014$), and sperm PR rate ($P < 0.000$) were all higher than in other seasons. The differences between the groups were significant, as illustrated in **Table 4**. However, the summer had lower levels of total sperm number, sperm concentration, and total sperm motility compared to the other seasons.

Table 4. Semen parameters according to the season

Seasons	Sperm concentration ($\times 10^6$/mL)	Total sperm number ($\times 10^6$/mL)	Sperm PR (%)	Total sperm motility (%)
Spring	79.72 ± 52.49	258.73 ± 178.41	43.08 ± 14.99	52.39 ± 26.35
Summer	75.83 ± 50.27	241.81 ± 179.43	42.18 ± 15.78	51.17 ± 17.49
Autumn	79.76 ± 50.63	259.81 ± 187.61	42.50 ± 14.76	51.79 ± 16.52
Winter	82.43 ± 50.85	274.08 ± 188.21	42.29 ± 15.15	50.33 ± 16.79
P	0.005	0.000	0.000	0.014

Displayed as the mean ± standard deviation, while $P < 0.05$ indicated statistically significant differences

4. Discussion

Researchers have extensively studied the factors that impact the outcomes of IVF-ET. Nevertheless, the specific underlying mechanisms remain unclear. These factors include etiology, number of retrieved eggs, infertility duration, cause of infertility, endocrine levels, number of transferred embryos, and transplantation technique [5]. Many agree that factors such as the female partner's age, the quantity of high-quality embryos, and endometrial receptivity significantly affect embryo implantation [14,15]. The outcomes of this study align with these findings. Age, endometrial thickness, and sperm PR rate were found to impact the clinical pregnancy rate during the ovarian retrieval cycle ($P < 0.05$) using MLR analysis, as presented in **Table 3**.

However, clinical and internal laboratory data limit the analysis of these factors. The impact of environmental factors on human ART has recently attracted increasing attention from researchers worldwide. According to previous research, fertilization and pregnancy rates in autumn and winter are substantially greater compared to those in the hot season [12]. At the same time, other researchers believe that fertilization rates do not fluctuate seasonally [3,12,16,17]. This research demonstrated that neither the clinical pregnancy rate, live birth rate, nor 2PN rate significantly differed among the ovarian retrieval cycles grouped by seasons, as shown in **Table 3**. This agrees with the findings of Wunder *et al.* [10]. Seasonal changes may impact clinical pregnancy outcomes, but differences in patient geographical location, climate, temperature, and lighting time contribute to varied research conclusions.

In the artificial insemination cycle, the winter season had the highest rates of clinical pregnancy and sperm PR, with significant differences ($P < 0.05$) between the groups, as illustrated in **Table 1**. Seasonal changes affect pregnancy outcomes in women undergoing ovarian retrieval cycles, with photoperiodicity being the primary environmental factor responsible for seasonal variations in mammalian reproduction [1,5]. This leads to seasonal variations in the pineal gland's melatonin secretion rhythm. The results of this study demonstrated that longer winter days result in higher melatonin secretion, which raises the number of mature oocytes, enhances fertilization rates, and produces more high-quality embryos [18-20].

Sperm and clinical pregnancy outcomes in both artificial insemination and ovarian retrieval cycles are correlated. To further verify these findings, we collected semen from outpatient patients for univariate analysis. This study discovered that total sperm concentration and total sperm number in winter were greater than those in other seasons. However, sperm concentration and total sperm number were lower in summer than in the other seasons (refer to **Table 4**). In general, these results agree with the outcomes of the majority of earlier research. Sperm concentration and total sperm count were also found to be significantly greater in winter compared to other seasons and lowest in summer, according to a study done in Shaanxi, China [21]. However, there are many contradictory findings regarding the effects of season on semen quality. According to a study done in Beijing, China, summer has higher sperm concentrations and counts overall [22].

This research has several limitations. Firstly, Hainan Province has a tropical monsoon marine climate with four vague seasons, neither extreme summer heat nor harsh winter cold. The average annual temperature is high, and the annual temperature range is small. Second, retrospective data were collected from a single center at the Reproductive Center of Hainan Women and Children's Medical Center, which may have affected the research results. Therefore, this article cannot be generalized to other climatically distinct areas.

5. Conclusion

The clinical pregnancy and live birth rates of artificial insemination in the Hainan region are affected by seasonal variations, while the rates of ovarian retrieval cycles remain unchanged. These findings suggest there is no need to choose a specific season when preparing for the ovarian retrieval cycle in the Hainan region. Hence, artificial insemination of patients can be optimized by selecting the winter season.

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The authors declare no conflict of interest.

Author contributions

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Ethics statement

The studies having human subjects were approved after being reviewed by the Ethics Committee of the Hainan Women and Children's Medical Center. Written informed consent was not required to participate in this study, as per institutional policies and national law.

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