There are no IUI pregnancies every year in the month of September. Why?

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Abstract

Introduction
The IUI pregnancy rate (PR) has been 0% in the month of September every year. We question why this is so? Could this be due to the very high ambient temperatures or other climatic conditions every year during the months of April through October in Dammam, Saudi Arabia?
Methods
To answer this question we investigated retrospectively the effect of ambient temperature of ≥37°C, ≥34°C and ≥31°C as well as humidity and barometric pressure on the monthly IUI PRs for three years beginning from 2017 through 2019.
Results
The pregnancy rate in the hot summer months of June to October were (4.9%; 13/263; Range: 0%-7.4%) compared to cooler months (12.3%; 77/624; Range: 9.3 to 20.5%; p=0.0009); but for September every year the PR was 0%. A highly significant negative correlation exists between ambient temperature ≥37°C, ≥34°C but not ≥31°C and the IUI PR.
Conclusion
The available evidence indicates that IUI pregnancies are affected by high ambient temperatures and its impact could last as long as 3 months following exposure to high ambient temperature ≥34°C. Patients must be counselled to refrain from exposure to high ambient temperatures at least 3 months prior to IUI and ART treatment to ward off the detrimental effects of high ambient temperatures in Dammam and in surrounding regions of similar geography. Patients must adhere to precautionary measures to avoid poor treatment outcome. Other regions of the world that experience extreme high ambient temperatures should take appropriate precaution or measures to avoid less optimal or futile IUI and ART treatments during months of extreme high ambient temperatures.

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Introduction

The IUI pregnancy rates have been 0% in the month of September every year for a number years in our assisted conception facility based in the city of Dammam, Kingdom of Saudi Arabia. We question why this is so? The most plausible reason appeared to be the very high ambient temperatures during the months of April through October which could be a contributory factor for the zero pregnancy rate in September every year. The highest daily temperature could reach 50°C during the hot season. It is well known the ambient temperature in the Arabian Peninsula is among the highest in the world.

The adverse effect of increased testicular temperature as a contributory factor on impaired spermatogenesis in agricultural animals is well documented. In most mammals the testes are located in the scrotum outside the body that provides the anatomic position that offers lower testicular temperature than the core body temperature. Although the external location of the testes makes the scrotal testes significantly cooler than the rest of the body however it does not keep it at a constantly lower temperature (Setchell, 1998), probably because it does not protect the testes from the insults of extreme environmental climatic conditions. It is now well recognized in mammals including human that the optimal spermatogenesis takes place in the testes at a temperature that is 2–6 °C lower than the body. If scrotal temperature rise above the physiological temperature of the testes, then spermatogenesis will be affected adversely (Mieusset and Bujan; Liu, 2010) resulting in a reduction in the spermatozoa count (Jannes et al., 1998; Pe´rez-Crespo et al., 2008) and accompanied by an impairment of sperm function (Fleming et al., 2004; Yaeram et al., 2006). More interestingly the work of Nakamura et al. has demonstrated that DNA synthesis in testicular tissue is significantly lower at 37^{o}C compared to 31^{o}C which suggest that spermatogenesis is better at lower temperature of 31^{o}C (Nakamura et al., 1987). Also, in the human spermatogenesis takes about 74 days (Amann, 2013) involving 4 distinct developmental processes. It would be of interest to determine at which developmental phase the detrimental effect of high ambient temperatures are most felt and profound.

It is assumed the high ambient temperature especially during the hot months of April through October may have impaired spermatogenesis in the IUI patients which is subsequently reflected in the pregnancy outcome following IUI treatment.

Therefore the questions were whether heat stress due to high ambient temperature has any influence on the IUI pregnancy rate? If so when will the detrimental effect be felt, immediately, or after one, two, or three months following onset of the high ambient temperatures? Also at what temperature the effect of high ambient temperature begins to affect IUI pregnancy? To answer these questions we have investigated the effect at ≥37^{o}C (that is above the body temperature), ≥34^{o}C (because the scrotal temperature has to be 2^{o}C to 6^{o}C below body temperature and ≥31^{o}C (since sperm DNA synthesis has been found to be better below this temperature (Nakamura et al., 1987). We investigated the effect of ambient temperature on the monthly IUI pregnancy rates for three years beginning from 2017 through 2019. Likewise, we also investigated the impact of other climatic conditions such as relative humidity and barometric pressure on the IUI pregnancy rates.

Materials and Methods

We retrospectively examined monthly IUI treatment outcome, specifically, the monthly pregnancy rates against the corresponding highest monthly ambient temperatures recorded for the years 2017 through 2019. The data on ambient temperatures were obtained from online resources (Dammam Climate, 2021).

Effect of specific temperatures on IUI pregnancy rate

Group 1: Comparison between ≤37^{o}C vs ≥38^{o}C

We have compared the effect of highest monthly ambient temperatures on the corresponding monthly IUI pregnancy rates. In Group 1 the cut off temperature is the physiological temperature of 37^{o}C. The pregnancy rates were compared between months that registered temperatures below ≤37^{o}C and those above ≥38^{o}C. To determine whether the detrimental effect of heat is immediate or occurs only after prolonged exposure to higher temperatures we also investigated the effect of heat on corresponding pregnancy rates one, two and three months after onset of higher ambient temperatures.

Group 2: Comparison between ≤33^{o}C vs ≥34^{o}C

In the human, the scrotal temperature is considered to be about 2^{o}C to 6^{o}C below the core body temperature. We have therefore compared the pregnancy rate obtained for months that registered temperatures below ≤33^{o}C and compared them with the pregnancy rate obtained in months that registered temperatures above ≥34^{o}C to elucidate whether the temperatures that simulate the scrotal temperature of about 4^{o}C below core body temperature (33^{o}C) will have an impact on the IUI pregnancy rate? The investigations performed in this group (Group2) were identical to that performed in Group 1.

Group 3: Comparison between ≤31°C vs ≥32°C

In addition we have also compared the pregnancy rate obtained for months that registered temperatures below ≤31°C and compared them with the pregnancy rate obtained in months that registered temperatures above ≥32°C to elucidate whether the suggestion (Nakamura et al. 2007) that sperm function could be affected if the temperature increased above 31°C. The investigations performed in this group (Group3) were identical to that performed in Group 1.

Statistical analysis

Pearson's linear regression analysis was performed to determine whether there is any correlation between high ambient temperatures and IUI pregnancy rates. The pregnancy rates between groups were statistically compared. All statistical analyses were performed by using the MEDCALC™ and STATISTIX™ statistical softwares.

Results

The highest daily ambient temperatures remained high, that is above physiological temperature (37°C), for the months of April through October (n=7 months) every year except in one instance March 2018 registered high temperature as well. Therefore high ambient temperatures could occur for 8 months in a year. The results pertaining to effect of temperature is given in detail in subsequent paragraphs. The relative humidity appears U-shaped with lowest levels seen in the hot months however there was almost but no correlation (r= 0.5612; p= 0.0576) between humidity and IUI pregnancy rate humidity. Likewise the barometric pressure is also u-shaped but although the changes in barometric are not very discernible but there is significant (r=0.664; p=0.0184) positive correlation between IUI pregnancy rate and barometric pressure (Table 1). Importantly the humidity and barometric pressures used were the monthly average figures calculated for 30 years from 1985 to 2015. If individual monthly humidity figures were used for years 2017 to 2019 it is likely the correlation between IUI pregnancy rate and relative humidity could become significant however these figures were not available to us.

In general the pregnancy rate in the hot summer months of June to October appear to be affected (4.9%; 13/263; Range: 0%-7.4%) compared to other months (12.3%; 77/624; Range: 9.3 to 20.5%; p=0.0009). The pregnancy rate for the month of September for all 3 years investigated remained consistently 0% for individual years investigated (Table 1).

The cumulative data for all three years is given in Table 2. The IUI pregnancy rates appear to improve immediately after the return of cooler temperatures in November every year (Table 2). It is also worth noting the average daily temperatures above ≥34°C occur from June to September for the study period. The confounding effect of no cases performed in the month of June 2017 and 2018 and only 7 cases in 2019 has been noted and taken into consideration to avoid misinterpretation of data.

Effect of specific temperatures on IUI pregnancy rate

The overall pregnancy rate for 3 years for months that registered monthly temperatures of ≤37°C (Group 1) was 13.4% (54/403) whereas for months with temperatures ≥38°C was 7.4% (36/484; p=0.0034; Table 3). For Group 3 the overall pregnancy rate for months that registered monthly daily temperatures of ≤31°C was 16.4% (32/195) whereas it was significantly lower at 8.4% (58/692; p=0.0010; Table 3) for months which had temperatures ≥32°C. There were no significant differences between the pregnancy rates at ≤31°C vs ≤37°C (13.4%, 54/403 vs 16.4%, 32/195; p=0.3274) or at ≥32°C and ≥38°C (7.4%, 36/484 vs 8.4%, 58/692; p=0.5338). A highly significant negative correlation exists between ambient temperature and the IUI pregnancy rate (r=-5019; p=0019; Table 3).

Effect of temperature on the IUI pregnancies 1 month after onset of high temperatures.

For Group 1 the pregnancy rate appears to be significantly affected one month after onset of the high temperature. If the cut-off point is 37°C then the overall pregnancy rate was 13.2% (55/416) whereas for months with temperatures ≥38°C it was significantly lower at 8.0% (35/436; p=0.0044; Table 3).

For Group 3, if 31^{o}C is taken as the cut-off point, the pregnancy rate was 13.5% (31/230) and this was statistically insignificantly lower for corresponding months with temperatures ≥32^{o}C, that is, 9.0% (59/657; p=0.0518; Table 3).

A highly significant negative correlation exists between ambient temperature with the pregnancy rate after IUI treatment (r= -4979; p=0020; Table 3).

Effect of temperature on the IUI pregnancies 2 months after onset of high temperatures.
For Group 1 the pregnancy rate appears to be significantly affected two months after onset of the high temperature. If the cut-off point is 37^{o}C then the overall pregnancy rate was 15.4% (62/465) whereas for corresponding months with temperatures ≥38^{o}C it was significantly lower at 7.0% (28/422; p=0.0010; Table 3).

Whereas for Group 3, if 31^{o}C is taken as the cut-off point, the pregnancy rate was 12.8% (30/234) and it was statistically insignificantly lower for the corresponding months with temperatures ≥32^{o}C that is, 9.2% (60/653; p=0.1144; Table 3).
A highly significant negative correlation exists between ambient temperature with the pregnancy rate after IUI treatment (r= -4641; p=0044; Table 3).

4. Effect of temperature on the IUI pregnancies 3 months after onset of high temperatures.
For Group 1 the pregnancy rate appears to be significantly affected three months after onset of the high temperature. If the cut-off point is 37^{o}C then the overall pregnancy rate was 12.7% (49/387) while for corresponding months with temperatures ≥38^{o}C it was significantly lower at ≥38^{o}C was 8.2% (41/500; p=0.0291; Table 3).
In Group3, if 31^{o}C is taken as the cut-off point, the pregnancy rate for the corresponding months was 9.8% (28/285) whereas for corresponding months with temperatures ≥32^{o}C it was statistically similar at 10.3% (62/602; p=0.8270; Table 3).

An insignificant negative correlation exists between ambient temperature with the pregnancy rate after IUI treatment (r= -3065; p=0690; Table 3).

Discussion

The present findings clearly indicate high ambient temperatures above ≥34oC are correlated with lower IUI pregnancy rates. Concerted effect of high ambient temperatures for up to three months appears to affect IUI pregnancies significantly with no (0%) pregnancies altogether in the month of September every year. The pregnancy rate in the hot summer months of June to October appear to be severely and significantly affected (4.9%) compared to cooler months (12.3%). It is not clear whether barometric pressure could impact the IUI pregnancy rate although there appears to be a significant positive correlation. Nevertheless the authors prefer not to speculate on this effect until the physiologic relationship between barometric pressure and pregnancy rate is elucidated. The authors are of the opinion the effect of barometric pressure on the IUI pregnancy rate is an artefact. The available data on humidity does not show a relationship to IUI pregnancy rates. Consequently the only explanation appears to be the high ambient temperatures. However the confounding factor is that all patients live in the comforts of climate-controlled air-conditioned homes and travel in air-conditioned vehicles, and thus presumably are protected from the detrimental effects of high ambient temperatures. What then is the real cause of the low or lack of no IUI pregnancies in the hot months observed every year?

Could some form of radiation during the hot months that could penetrate walls of homes and surfaces of vehicles during the hot months cause heat stress that ultimately affect IUI pregnancies? This may sound unreasonable but heat radiating from heated walls of dwellings is known to cause considerable discomfort to occupants of such homes in spite of their use of air-conditioners even though it offers fairly good climate-control in the dwellings. If this is so then natural conception too should be low in the hot months leading to lower natural fecundity rate for conceptions that take occur in the hot months.

In addition it must be borne in mind that seats of parked vehicles are almost always very hot especially since the ambient temperatures could be anywhere between 40 to 50^{o}C in the hot

Table 1: Monthly IUI pregnancy rates and its corresponding highest monthly ambient temperatures for years 2017 through 2019.

Description	2017		2018		2019	
	Pregnancy %	High. Temp °C*	Pregnancy %	High. Temp °C	Pregnancy %	High. Temp °C
Jan	7% (1/15)	28	5% (1/20)	27	16% (5/31)	**28**
Feb	29% (4/14)	27	17% (7/41)	32	21% (10/47)	**26**
Mar	6% (2/33)	36	10% (5/52)	39	13% (3/23)	**30**
Apr	17% (5/30)	43	9% (4/46)	40	8% (3/37)	**41**
May	11% (3/27)	46	8% (2/25)	46	25% (1/4)	**47**
Jun	0% (0/0)	50	0% (0/0)	47	0% (0/8)	49
Jul	0% (0/17)	49	10%(3/29)	47	9% (2/22)	**48**
Aug	5% (1/25)	47	0% (0/12)	48	17% (1/6)	**48**
Sep	0% (0/7)	47	0% (0/28)	45	0% (0/24)	**48**
Oct	0% (0/27)	41	11% (4/37)	43	8% (2/25)	**44**
Nov	8% (3/37)	34	14% (6/42)	33	11% (3/27)	**33**
Dec	22% (5/23)	30	14% (3/22)	27	4% (1/28)	**32**
Total	10% (24/251)	39.8	10% (35/354)	39.5	11% (31/282)	**39.5**

https://www.timeanddate.com/weather/saudi-arabia/dammam/historic?month=6&year=2017

Table 2: Cumulative monthly IUI pregnancy rates and its corresponding ambient temperatures for years 2017 through 2019.

Description	% IUI Pregnancy	Highest Temp^{o}C	Lowest Temp^{o}C	*Average daily Temp^{o}C	** % average monthly relative humditiy	**Barometric pressure (mbar)
Jan	10.6% (7/66)	21	11	16	68	1018
Feb	20.5% (21/102)	23	13	18	63	1016
Mar	9.3% (10/108)	39	16	21.5	54	1013
Apr	10.6% (12/113)	41	21	27	45	1010
May	10.7% (6/56)	46.3	26	33*	35	1005
Jun	0% (0/8)#	48.7	28	35.5*	29	1000
Jul	7.4% (5/68)	48	30	37*	34	996
Aug	5.1% (2/39)	47.7	30	36.5*	45	998
Sep	0% (0/59)	46.7	27	34*	49	1004
Oct	7% (6/89)	44	23	29.5	58	1011
Nov	11.3% (12/106)	34	18	23.5	62	1015
Dec	12.3% (9/73)	24	13	18.5	67	1018
Total	10.1% (90/887)	33.7	21.3	27.5	51	1009

https://www.timeanddate.com/weather/saudi-arabia/dammam/historic?month=6&year=2017
very few cases in June for all three years.
*Temperatures above 31^{o}C is detrimental for sperm DNA synthesis

Table 3: Effect of ambient temperature on the pregnancy rate following IUI treatment in Dammam, Saudi Arabia (2017-2019)

Treatment/ Description	Group 1: Pregnancy rate if cut-off point is 37°C (p-value)		Group 2: Pregnancy rate if cut-off point is 33°C (p-value)		Group 3: Pregnancy rate if cut-off point is 31°C (p-value)		Correlation r-value: Pregnancy rate vs temperature
Effect of duration of high temp	**≤37°C**	**≥38°C**	**≤33°C**	**≥34°C**	**≤31°C**	**≥32°C**	**r-value (p-value)**
0 Month/ Immediate effect	13.40% 54/403	7.40% 36/484 (p=0.0034)	14.7% 49/333	7.4% 41/554 (p=0.0005)	16.40% 32/195	8.40% 58/692 (p=0.0010).	r= -5019 (p=0019)
≥ Effect after 1 month	13.20% 55/416	8.00% 35/436 (p=0.0044).	12.4% 45/363	8.6% 45/524 (p=0.0647)	13.50% 31/230	9.00% 59/657 (p=0.0518)	r= -4979 (p=0020)
≥ Effect after 2 months	15.40% 62/465	7.00% 28/422; (p=0.0010)	13.2% 50/378	7.9% 40/509 (p=0.0088)	12.80% 30/234	9.20% 60/653 (p=0.1144	r= -4641 (p=0044)
≥ Effect after 3 months	12.70% 49/387	8.20% 41/500 (p=0.0291).	12.1% 45/373	8.6% 45/514 (p=0.0421	9.80% 28/285	10.3% 62/602 (p=0.8270).	r= -3065 (p=0690).

months in Dammam beginning from early hours at the beginning of and well beyond office hours. The seats will get heated when left parked in open car parks for long hours. Open car parks are the most common form of car parks available in Dammam. Moreover some parking lots that are covered are however exposed to the elements and are not climate-controlled. Such car parks too are the second most common forms of car parks in Dammam. The seats of cars parked in such parks could also get heated up. Seats that have been heated up will not cool down for a long time even though the air-condition of the car has been put on soon after the car engine has been turned on. It appears reasonable to speculate the heated seats of cars can damage spermatogenesis when men are exposed to such conditions on a regular basis. Covered climate-controlled car parks are extremely rare and are not available to a vast majority of the population in Dammam. It therefore follows that this factor could be the most plausible of the causative factors for the low or paucity of IUI pregnancies in the hot months.

The present study does not have any data that could suggest which of the four developmental stages (Amann, 2013) of spermatogenesis is compromised or affected by high ambient temperatures? However a recent study by Abdelhamid and coworkers (Abdelhamid et al., 2019) that investigated a mild increased in scrotal temperature may provide some answers to these questions. Mild increase in scrotal temperature for 120 days had major but reversible consequences in men. The scrotal temperature in the study temperature was increased slightly to not more than body temperature by using specially designed underwear. In the test group, at 34 days of exposure to mild increase in scrotal temperature had no effect on sperm aneuploidy. Interestingly there was a drastic drop in sperm count from days 34 to 45 which made aneuploidy investigation by FISH technic not possible. However by 45 days of post increased scrotal temperature the sperm aneuploidy rate had increased twice it was before heating commenced. Furthermore sex disomy (sperm XY18) and sex chromosome nullisomy (sperm

18) were significantly higher than controls. However all these effects were completely reversed at 180 days post cessation of heat exposure meaning that it took more than two cycles of spermatogenesis to recover from the harmful effects of heat stress. Similar observations suggesting scrotal hyperthermia can alter sperm chromatin has been reported (Ahmad et al., 2012 and Niederberger 2012).

The detrimental effect of heat is thought to occur during the meiotic stage of spermatogenesis (Abdelhamid et al., 2019) which is the second stage in the development and maturation of sperm during spermatogenesis (Amann ,2008). It is known that most chromosomal abnormalities in sperm occur as a consequence of errors that occur during the meiotic stage of spermatogenesis (Griffiths and Suzuki, 2000; Uroz and Templado, 2012). In the present study the impact of temperatures higher than ≥34^{o}C can be felt well into the third month after exposure whereas the detrimental impact of heat when exposed to ≥32^{o}C is short-lived and is felt immediately but not beyond the first 30 days of exposure. The reason for this effect is not clear. It could only be speculated that the impact of heat at ≥32^{o}C probably is not as severe compared to exposures to heat at ≥34^{o}C.

It has been demonstrated that transient scrotal hyperthermia affects negatively spermato-genesis and causes oxidative stress significantly, but this is reversible (Rao et al. 2015). Moreover intermittent exposure to heat more effectively suppresses spermatogenesis than consecutive heat exposure (Rao et al. 2015) but the reason for this is not clear. Moreover there is evidence that showed that heat shock treatment at 43°C for 45 min significantly inhibited spermatogonial stem cell self-renewal (Wang et al., 2019) . Heat stress affecting the scrotum can lead to excessive production of reactive oxygen species which could lead to apoptosis of the spermatozoa (Yin et al., 1997; Lue et al.,1999; Agarwal et al., 2014; Rao et al., 2015).

It is also not clear whether heat stress that occurs as a consequence of high ambient temperature could also affect the capability and viability of mammalian, and in the current context, human oocytes? If so what detrimental effects could it have on pregnancies and on the offspring?

In neighbouring Qatar, studies by Ali and coworkers (Ali et al., 1999) reported that high ambient temperatures during the hot months had no effect on conventional IVF fertilization rate but ICSI fertilization rate was significantly lower during the hot months. They also noted that the zygote cleavage rate was significantly lower and day 2 embryo quality was significantly poorer in the hot months. Although the pregnancy rate was identical however the abortion rate was higher for conceptuses initiated in the hot months. We have observed a similar outcome for cIVF and ICSI in our center but this study has not been completed as yet. Qatar and Dammam share the same geographical features. Qatar is directly south of Dammam. The present findings as well as those described in preceding discussion suggest high ambient temperatures, including transient exposures of the scrotum to high temperatures of heated car seats, have a negative impact on IUI and ART treatment. Considering the emotion-charged sequelae and the very high expectations experienced by ART patients post treatment, the present findings and that of others described herein raises the question how IUI and ART can be performed without suffering the consequences of the detrimental effect of poor pregnancy rate in the hot months in Dammam? Obviously, counselling patients to refrain from exposure to high ambient temperatures including regular drives in cars with heated seats in the hot months appears paramount to avoid the poor outcome after IUI and ART treatments. Service provider must counsel patients to refrain from exposure at least 3 months prior to IUI and ART treatment to ward off the detrimental effects of high ambient temperatures in Dammam and in surrounding regions of similar geography. Patients must adhere to precautionary measures. Other regions of the world that experience extreme high ambient temperatures should take appropriate precaution or measures to avoid less optimal or futile IUI and ART treatments during months of extreme high ambient temperatures.

Conclusion

In conclusion, the scientific evidence available has shown that IUI pregnancies are affected by high ambient temperatures. The impact of this form of heat stress could last as long as 3 months following exposure to high ambient temperature ≥34°C. Patients must be counselled to refrain from exposure to high ambient temperatures at least 3 months prior to IUI and ART treatment in Dammam and in surrounding regions of similar geography. Other regions of the world that experience extreme high ambient temperatures should take appropriate precaution or measures to avoid less optimal or futile IUI and ART treatments during months of extreme high ambient temperatures.

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