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Temporal effect of maternal heat stress during gestation on the fertility and anti-Müllerian hormone concentration of offspring in bovine

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ABSTRACT

Ovarian reserve has been suggested as an important contributing factor of reproductive success in bovine. Size of ovarian reserve is determined during fetal period and it could be altered by environmental factors, with which the dam is exposed. Maternal heat stress could impair placental function and fetal development; however, there is limited information on the impact of prenatal heat stress on fertility and ovarian reserve in the offspring. Therefore, a retrospective study was conducted, in which fertility parameters and AMH concentration, as a reliable marker of ovarian reserve in bovine, were studied in the offspring of dams that had been exposed to heat stress during the first (FTE), second (STE) or third (TTE) trimester of gestation and the offspring of dams unexposed to heat stress (US). Additionally, postpartum exposure of offspring with heat stress was considered in the model to adjust the statistical analysis in this regard. Days to first service (DFS) and calving to conception interval (CCI) were prolonged in exposed than unexposed cows ($P < 0.05$). Days to first service and CCI were also longer in STE compared with FTE cows ($P < 0.05$). First service conception rate was lower in TTE than UN cows ($P < 0.05$). The proportion of repeat breeders was higher in exposed compared with unexposed cows ($P < 0.05$). Service per conception was higher in STE and TTE than UN cows ($P < 0.05$). Culling rate between different periods of lactation was also higher in exposed than unexposed cows ($P < 0.05$). Finally, AMH concentration was lower in STE and TTE than UN cows ($P < 0.05$); moreover, it was lower in STE compared with FTE cows ($P < 0.05$). In conclusion, the present study revealed detrimental effects of maternal heat stress on fertility, productive longevity and ovarian reserve in the offspring. In this context, the second and third trimesters appeared to be more critical periods.

1. Introduction

The size of ovarian reserve, the number of primordial follicles, has been observed to be associated with fertility in bovine [1–3]. Cows with low ovarian reserve have low oocyte quality [4], reduced embryonic developmental competence [5], low progesterone concentration [6], impaired endometrial growth [6] and earlier ovarian senescence [7]. As a result, lower pregnancy rates [1,2], higher service per conception [1], longer calving to conception interval [1] and shorter productive life [3] have been reported in cows with low ovarian reserve.

The formation of ovarian reserve occurs during fetal life in bovine [8,9]. Although the size of ovarian reserve is influenced by genetic factors [10], compelling evidence indicates that maternal environmental factors during pregnancy could substantially impact the size of ovarian reserve in the female offspring in bovine [11] as well as other mammals [12–16].

It is well-established that heat stress adversely affects reproduction in mammals including cattle [17,18]. Exposure to heat stress would impair oocyte competence [19] and disrupt early embryonic development [20]. Moreover, heat stress causes reduced fetal and placental weight [21], and concentrations of placental hormones [22]. Maternal exposure to heat stress during gestation has also been observed to compromise the growth and immune function of calves [23,24]. Furthermore, heifers born to cows exposed to heat stress during late gestation have been observed

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with more service per conception [24]. Nevertheless, the effect of maternal heat stress exposure during different stages of pregnancy on fertility and ovarian reserve of the subsequent offspring has not been investigated to our knowledge.

Anti-Müllerian hormone (AMH) is a member of transforming growth factor β superfamily, which is primarily secreted by granulosa cells of healthy growing follicles [25]. Circulating AMH concentration is highly positively associated with ovarian reserve in bovine [26,27], human [25] and murine [28], and has minimal day-to-day variation within individuals over the course of reproductive cycles in bovine [27,29] and human [30]. Therefore, a single measurement of AMH obtained on any day of the estrous cycle has been reasonably proposed to serve as a reliable phenotypic marker for ovarian reserve in cattle [27].

Accordingly, a retrospective study was performed to assess the effects of maternal exposure to heat stress during different trimesters of pregnancy on reproductive performance and AMH concentration in the next generation.

2. Materials and methods

2.1. Animals, location, climatic data

Animal Ethics Committee at University of Tehran approved the present study in terms of animal welfare and ethics.

The present study was conducted at a commercial Holstein dairy farm located in Varamin county, Tehran province, Iran (Latitude: 35° 46′ N; Longitude: 51° 65′ E; Altitude: 1200 m) with arid climate. Based on climatic data, cows were exposed to heat stress (temperature humidity index ≥ 72) [31] in June, July and August over the last 15 years (2001–2015; Fig. 1). Temperature-humidity index (THI) was calculated as follows: THI = dry bulb temperature + (0.36 − dew point temperature) + 41.2 [32]. In the herd, voluntary waiting period was 42 days and cows were inseminated 12 h after the observation of standing estrus. Estrus detection was performed thrice daily by visual observation for at least 30 min each time. All artificial inseminations were conducted by the same technician and pregnancy diagnosis was performed 40–45 days after AI by transrectal palpation.

2.2. Data

To investigate the effect of maternal exposure during different trimesters of gestation, we assumed that in addition to exposure, time of exposure would be of significance. As a result, our inclusion criteria was to choose the female calves of dams that had been exposed to heat stress for ≥2.5 months during the first, second or third trimester of pregnancy. Additionally, to ease the data collection and analysis, the length of gestation in bovine was considered nine months, and months 1–3, 4–6 and 7–9 were presumed as the first, second and third trimester of pregnancy, respectively. Time of successful insemination was considered as the commencement of conception; therefore, cows that had been conceived from June 1 to 15 were considered as first trimester exposed; cows that had been conceived from March 1 to 15 were considered as second trimester exposed; cows that had been conceived from December 1 to 15 were considered as third trimester exposed; and cows that had been conceived from September 1 to 15 were considered as unexposed. Data associated with calves conceived from 2003 to 2007 were collected from the herd database. Since we intended to investigate fertility parameters in the same population of each group over the first, second, third and fourth lactation periods, cows with missed data in this regard were excluded from the analysis. In total, data consisted of 206 cows, out of which 42, 61, 55 and 48 cows belonged to unexposed, first trimester exposed, second trimester exposed and third trimester exposed groups, respectively. Given that offspring in various aforementioned categories of the present study were born at different times of year and the corresponding difference would probably lead to disparity in time of calving and postpartum breeding among different groups and considering the adverse effects of heat stress on fertility of cows [17,18], data associated with heat stress exposure of the offspring at the termination of VWP (Day 42 postpartum) were collected as well to avoid this confounding effect and adjust the statistical analysis in this regard.

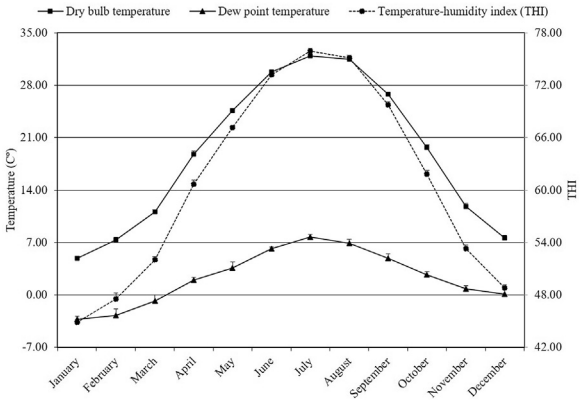

Fig. 1. Mean values for dry bulb temperature, dew point temperature and THI in different month from 2001 to 2015. Data were retrieved from the nearest meteorological station.

2.3. Reproductive parameters

Days to first service (DFS) was defined as the interval from parturition to first insemination. First service conception rate (FSCR) was defined as the proportion of cows diagnosed pregnant following first insemination postpartum. Cows that failed to conceive after 3 services were considered as repeat breeder (RB) cows. Service per conception (SPC) was defined as the number of services implemented to achieve conception in cows. Calving to conception (CCI) interval was defined as the number of days from parturition to conception. Days to first service, FSCR, RB, SPC and CCI were calculated using the data of cows diagnosed pregnant and the data of cows failed to conceive were not considered for calculation of the respective parameters. Culling rate (CR) was defined as the proportion of cows that failed to enter the next lactation period.

2.4. AMH assay

As aforementioned, cows with different history of prenatal exposure to heat stress were randomly subjected to blood sampling from various periods of lactation including the first, second, third and fourth periods. Cows received two administrations of PGF2α (500 μg i.m.; Vetaprost®; Aburaihan Pharmaceutical Co., Tehran, Iran) 14 days apart beginning at day 28 postpartum. Afterwards, cows were monitored for detection of standing estrus, and blood samples were taken using venipuncture from tail vein of cows observed in estrus. Blood samples were centrifuged for 10 min at 2000 × g within 2 h after collection. Serum was stored at −20 °C until hormonal assay. AMH concentration was measured using AMH (Bovine) ELISA kit (Ansh Labs, TX, USA). In addition, data associated with heat stress exposure at the time of blood

collection was recorded to adjust the statistical analysis in this regard.

2.5. Statistical analysis

Continuous data including weight at birth, SPC and AMH concentration were analyzed by linear regression using GLM procedure. Binary data including FSCR, RB and CR were analyzed by logistic regression using GENMOD procedure including function link logit in the model. Logistic regression analysis produced adjusted odds ratio (AOR) as the strength of difference between groups. Time-to-event data including DFS and CCI were analyzed using LIFETEST procedure. The hazard of insemination and conception were analyzed by Cox regression using PHREG procedure, in which cows that had been culled were censored. Cox regression analysis generated adjusted hazard ratio (AHR) as the conditional daily probability of the event (insemination or conception). In all fertility-associated analyses, exposure of offspring to heat stress at the end of VWP (Day 42 postpartum) was considered as a fixed effect in the model. In the analyses of AMH concentration, exposure to heat stress at the time of blood sampling was considered as a fixed effect in the model. LSMEANS statement was used to perform multiple comparisons. All analyses were conducted in SAS [33]. Differences were considered statistically significant at $P \leq 0.05$.

3. Results

3.1. Birth weight

Birth weight in unexposed, first trimester exposed, second trimester exposed and third trimester exposed groups were 41.86 ± 0.56 Kg, 41.16 ± 0.59 Kg, 41.31 ± 0.52 Kg and 39.60 ± 0.56 Kg, respectively. Birth weight in third trimester exposed group was lower than that in unexposed group ($P = 0.029$), but it did not differ among other groups ($P > 0.05$).

3.2. Fertility during the first lactation

3.2.1. Maternal heat stress exposure

The hazard of insemination was reduced in cows exposed to heat stress during the first (AHR = 0.780; 95% confidence interval [CI] = 0.673–0.903; P = 0.001), second (AHR = 0.524; 95% CI = 0.408–0.673; P < 0.0001) and third (AHR = 0.339; 95% CI = 0.209–0.547; P < 0.0001) trimester of pregnancy compared with unexposed cows (Fig. 2), which led to longer DFS in the first, second and third trimester exposed cows than in unexposed ones (P < 0.05; Table 1). Moreover, the hazard of insemination in the second trimester exposed cows was lower than that in the first trimester exposed ones (AHR = 0.630; 95% CI = 0.420–0.944; P = 0.025), which was also reflected in DFS (P = 0.001; Table 1). First service conception rate was lower in the third trimester exposed cows than unexposed ones (AOR = 0.328; 95% CI = 0.117–0.921; P = 0.034; Table 1). The proportion of repeat breeder cows was higher in the second (AOR = 3.437; 95% CI = 1.205–9.805; P = 0.021) and third (AOR = 3.398; 95% CI = 1.204–9.589; P = 0.021) trimester exposed cows compared with unexposed ones (Table 1). Service per conception did not differ among groups (P > 0.05; Table 1). The hazard of conception was lower in the second (AHR = 0.733; 95% CI = 0.586–0.918; P = 0.007) and third (AHR = 0.557; 95% CI = 0.358–0.866; P = 0.009) trimester exposed cows than in unexposed ones (Fig. 3), culminating in longer CCI in the second and third trimester cows than in unexposed ones (P < 0.05; Table 1). In addition, the hazard of conception was lower in the second than first trimester exposed

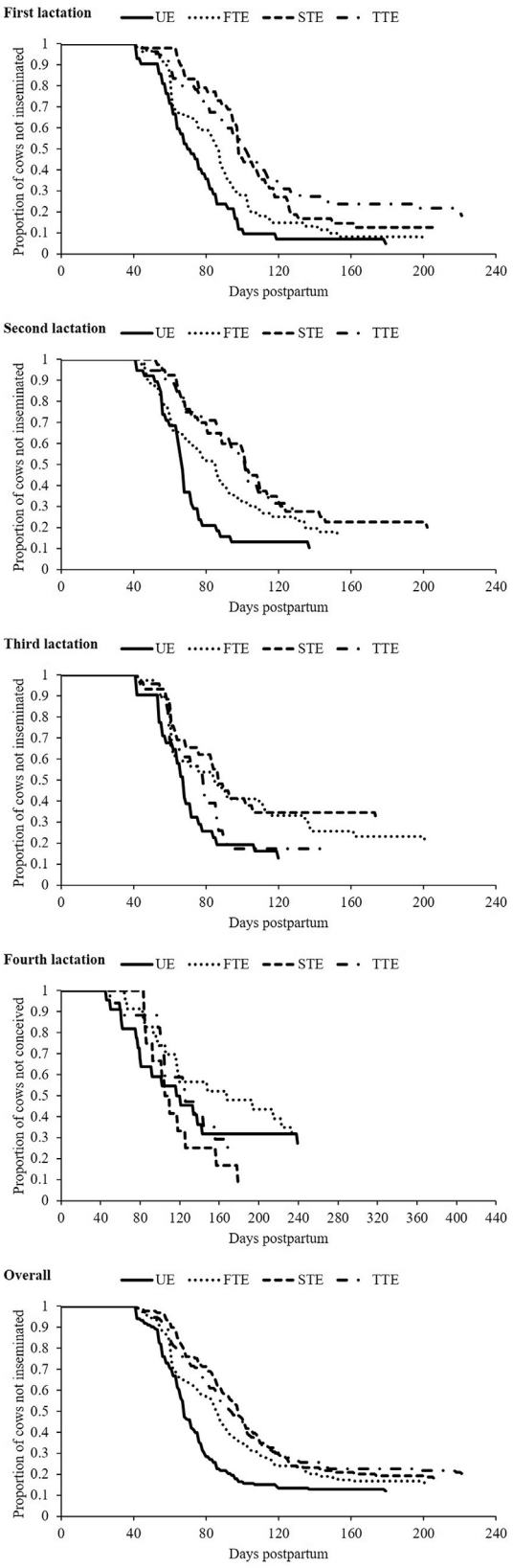

Fig. 2. Time to first insemination in female offspring during the first, second, third and fourth periods of lactation, and overall considering prenatal heat stress exposure during different trimesters of gestation, including unexposed (UN), first trimester exposed (FTE), second trimester exposed (STE) and third trimester exposed (TTE).

Table 1
Reproductive performance of female offspring over the first, second, third and fourth lactations in addition to overall reproductive performance of female offspring during four consecutive lactation periods considering prenatal heat stress exposure during different trimesters of gestation, including unexposed, first trimester exposed, second trimester exposed and third trimester exposed. Data are presented as mean ± SEM and percentages. Numbers in parenthesis are actual numbers.

Number of lactation	Parameter	Unexposed	First trimester exposed	Second trimester exposed	Third trimester exposed
First lactation		n = 42	n = 61	n = 55	n = 48
	DFS (day)	74.23 ± 3.91^{a}	85.39 ± 3.88^{b}	100.23 ± 4.47^{c}	98.69 ± 5.93^{bc}
	FSCR (%)	37.50 (15/40)^{a}	29.82 (17/57)^{ab}	27.91 (12/43)^{ab}	17.78 (8/45)^{b}
	RB (%)	17.50 (7/40)^{a}	29.82 (17/57)^{ab}	39.53 (17/43)^{b}	40.00 (18/45)^{b}
	SPC	2.35 ± 0.22	2.74 ± 0.21	3.05 ± 0.27	3.04 ± 0.21
	CCI (day)	132.55 ± 12.00^{a}	142.91 ± 8.56^{ab}	177.72 ± 12.31^{c}	173.31 ± 10.34^{bc}
	CR (%)	9.52 (4/42)^{a}	8.20 (5/61)^{a}	16.67 (8/48)^{ab}	30.91 (17/55)^{b}
Second lactation		n = 38	n = 56	n = 38	n = 40
	DFS (day)	67.09 ± 2.94^{a}	79.45 ± 4.13^{ab}	94.72 ± 5.64^{b}	87.54 ± 4.38^{b}
	FSCR (%)	41.18 (14/34)	36.17 (17/47)	28.13 (9/32)	21.43 (6/28)
	RB (%)	11.76 (4/34)	14.89 (7/47)	15.63 (5/32)	28.57 (8/28)
	SPC	2.00 ± 0.19^{a}	2.19 ± 0.18^{ab}	2.56 ± 0.29^{ab}	3.07 ± 0.41^{b}
	CCI (day)	101.09 ± 8.73^{a}	118.68 ± 8.62^{ab}	147.09 ± 11.34^{b}	150.04 ± 15.11^{b}
	CR (%)	18.42 (7/38)^{a}	30.36 (17/56)^{ab}	27.50 (11/40)^{ab}	39.47 (15/38)^{b}
Third lactation		n = 31	n = 39	n = 23	n = 29
	DFS (day)	66.74 ± 3.43	85.03 ± 6.68	78.35 ± 6.40	74.65 ± 4.85
	FSCR (%)	44.44 (12/27)	38.71 (12/31)	45.00 (9/20)	40.00 (8/20)
	RB (%)	3.70 (1/27)	6.45 (2/31)	5.00 (1/20)	5.00 (1/20)
	SPC	1.78 ± 0.19	1.90 ± 0.19	1.85 ± 0.21	1.90 ± 0.20
	CCI (day)	90.56 ± 7.77^{a}	120.35 ± 9.30^{b}	115.05 ± 16.17^{ab}	101.50 ± 8.20^{ab}
	CR (%)	29.03 (9/31)^{a}	41.03 (16/39)^{ab}	58.62 (17/29)^{b}	26.09 (6/23)^{a}
Fourth lactation		n = 22	n = 23	n = 17	n = 12
	DFS (day)	67.31 ± 3.51	85.06 ± 5.58	85.55 ± 6.4	77.92 ± 7.28
	FSCR (%)	50.00 (8/16)	50.00 (8/16)	36.36 (4/11)	38.46 (5/13)
	RB (%)	6.25 (1/16)	31.25 (5/16)	9.09 (1/11)	15.38 (2/13)
	SPC	1.88 ± 0.29	2.44 ± 0.45	2.00 ± 0.36	2.23 ± 0.36
	CCI (day)	101.25 ± 12.03^{a}	133.44 ± 4.16^{b}	113.18 ± 9.26^{ab}	113.46 ± 9.51^{ab}
	CR (%)	52.94 (9/22)	52.17 (12/23)	33.33 (4/12)	47.06 (8/17)
Overall		n = 133	n = 179	n = 133	n = 129
	DFS (day)	69.48 ± 1.84^{a}	83.43 ± 2.44^{b}	92.92 ± 2.92^{c}	86.66 ± 3.16^{bc}
	FSCR (%)	41.88 (49/117)^{a}	35.76 (54/151)^{ab}	32.08 (34/106)^{ab}	25.47 (27/106)^{b}
	RB (%)	11.11 (13/117)^{a}	20.53 (31/151)^{b}	22.64 (24/106)^{b}	27.36 (29/106)^{b}
	SPC	2.05 ± 0.11^{a}	2.36 ± 0.12^{ab}	2.57 ± 0.16^{b}	2.74 ± 0.16^{b}
	CCI (day)	109.44 ± 5.58^{a}	129.74 ± 4.89^{b}	149.95 ± 7.23^{c}	146.27 ± 6.78^{bc}

DFS: Days to first service; FSCR: first service conception rate; RB: repeat breeder cows; SPC: service per conception; CCI: calving to conception interval; CR: culling rate.
^{a,b,c}Values with different superscripts within rows differ (P < 0.05).

cows (AHR = 0.611; 95% CI = 0.406–0.921; P = 0.019; Fig. 3); as a result, CCI was prolonged in the second trimester exposed cows as compared with the first trimester exposed ones (P = 0.006; Table 1). Culling rate was higher in the third trimester exposed cows than unexposed (AOR = 4.380; 95% CI = 1.340–14.311; P = 0.015) and the first trimester exposed (AOR = 4.749; 95% CI = 1.605–14.049; P = 0.005) cows (Table 1).

3.2.2. Exposure to postpartum heat stress

The hazard of insemination was lower in heat stressed cows than unexposed ones (AHR = 0.424; 95% CI = 0.305–0.591; P < 0.0001; Fig. 4), causing prolonged DFS in exposed than unexposed cows (P < 0.0001; Table 2). First service conception rate was diminished in heat stressed than unstressed cows (AOR = 0.251; 95% CI = 0.103–0.614; P = 0.002; Table 2). The proportion of repeat breeders was higher in heat stress exposed than unexposed cows (AOR = 2.715; 95% CI = 1.365–5.400; P = 0.004; Table 2). Service per conception was higher in exposed than unexposed cows (P = 0.001; Table 2). The hazard of conception was reduced in heat stressed than unstressed cows (AHR = 0.498; 95% CI = 0.361–0.689; P < 0.0001; Fig. 5), leading to longer CCI in heat stress exposed than unexposed cows (P < 0.0001; Table 2). Culling rate did not differ between two groups (P > 0.05; Table 2).

3.3. Fertility during the second lactation

3.3.1. Maternal heat stress exposure

The hazard of insemination was lower in the first (AHR = 0.826; 95% CI = 0.704–0.969; P = 0.019), second (AHR = 0.542; 95% CI = 0.409–0.718; P < 0.0001) and third (AHR = 0.380; 95% CI = 0.216–0.669; P = 0.001) trimester exposed cows than unexposed ones (Fig. 2), which led to longer DFS in the second and third trimester exposed cows than unexposed ones (P < 0.001) but DFS did not statistically differ between the first trimester exposed and unexposed cows (P > 0.05; Table 1). First service conception rate and the proportion of repeat breeders did not differ among various groups (P > 0.05; Table 1). Service per conception was higher in the third trimester exposed than unexposed cows (P = 0.035; Table 1). The hazard of conception in the second (AHR = 0.687; 95% CI = 0.534–0.884; P = 0.004) and third (AHR = 0.503; 95% CI = 0.298–0.850; P = 0.010) trimester exposed cows was reduced compared with unexposed cows (Fig. 3), resulting in longer CCI in the second and third trimester exposed than unexposed cows (P < 0.05; Table 1). Culling rate was higher in the third trimester exposed than unexposed cows (AOR = 2.888; 95% CI = 1.014–8.227; P = 0.047; Table 1).

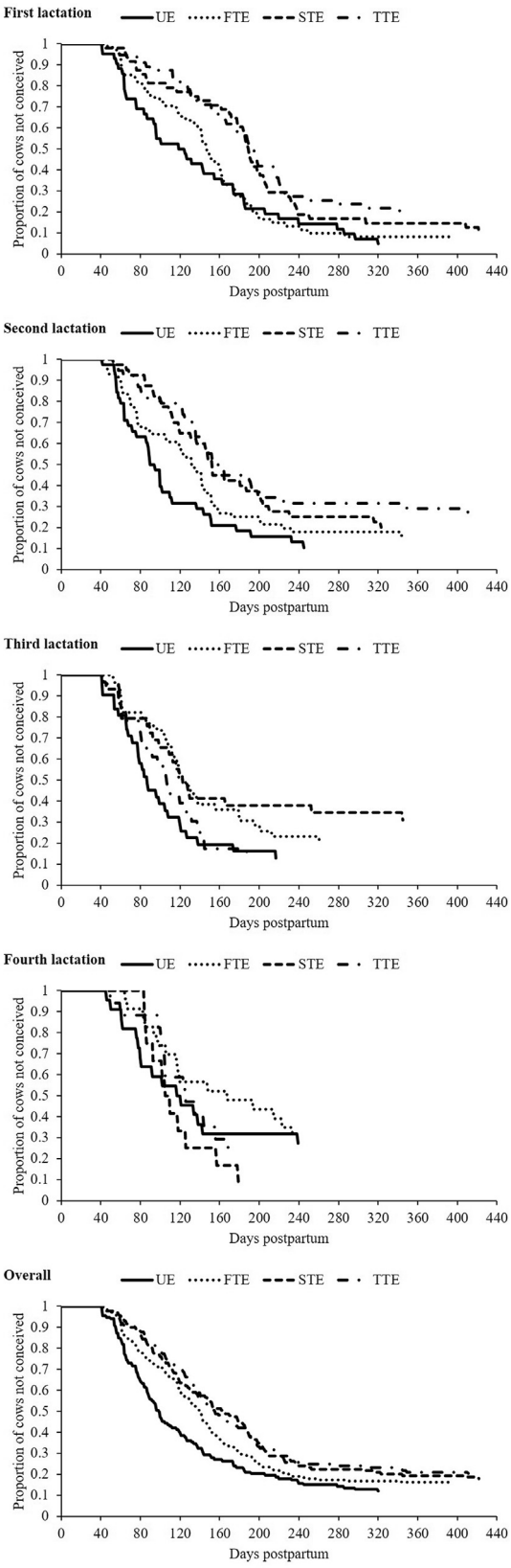

Fig. 3. Time to conception in female offspring during the first, second, third and fourth periods of lactation, and overall considering prenatal heat stress exposure during different trimesters of gestation, including unexposed (UN), first trimester exposed (FTE), second trimester exposed (STE) and third trimester exposed (TTE).

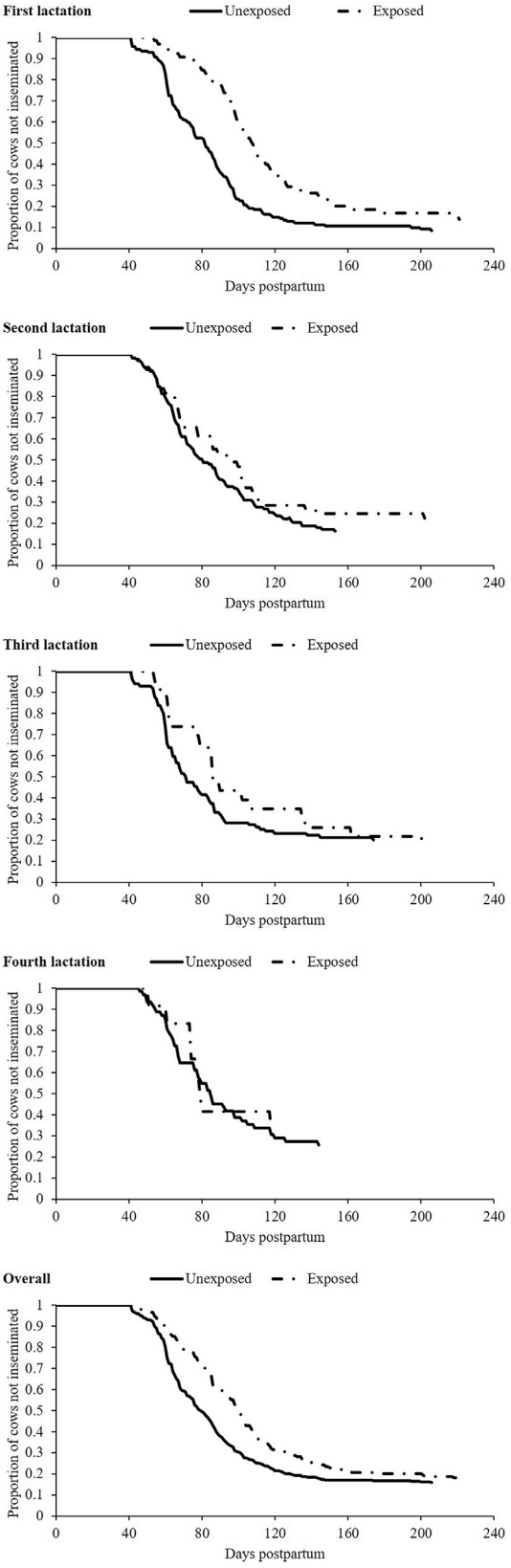

Fig. 4. Time to first insemination in female offspring unexposed and exposed to postpartum heat stress during the first, second, third and fourth periods of lactation, and overall.

Table 2
Reproductive performance of female offspring over the first, second, third and fourth lactations in addition to overall reproductive performance of female offspring considering postpartum heat stress exposure. Data are presented as mean ± SEM and percentages. Numbers in parenthesis are actual numbers.

Number of lactation	Parameter	Unexposed	Exposed
First lactation		n = 141	n = 65
	DFS (day)	81.60 ± 2.52[a]	108.23 ± 4.55[b]
	FSCR (%)	34.88 (45/129)[a]	12.5 (7/56)[b]
	RB (%)	25.58 (33/129)[a]	46.43 (26/56)[b]
	SPC	2.54 ± 0.14[a]	3.39 ± 0.17[b]
	CCI (day)	137.32 ± 6.42[a]	199.55 ± 7.61[b]
	CR (%)	14.18 (20/141)	21.54 (14/65)
Second lactation		n = 123	n = 49
	DFS (day)	80.17 ± 2.56	85.24 ± 5.12
	FSCR (%)	35.92 (37/103)	23.68 (9/38)
	RB (%)	16.50 (17/103)	18.42 (7/38)
	SPC	2.37 ± 0.16	2.50 ± 0.21
	CCI (day)	124.03 ± 6.77	135.47 ± 9.07
	CR (%)	29.27 (36/123)	28.57 (14/49)
Third lactation		n = 99	n = 23
	DFS (day)	72.28 ± 2.67	94.11 ± 9.03
	FSCR (%)	46.84 (37/79)[a]	21.05 (4/19)[b]
	RB (%)	3.80 (3/79)	10.53 (2/19)
	SPC	1.75 ± 0.10[a]	2.32 ± 0.24[b]
	CCI (day)	100.52 ± 5.74[a]	135.05 ± 10.97[b]
	CR (%)	42.42 (42/99)	26.09 (6/23)
Fourth lactation		n = 63	n = 11
	DFS (day)	78.48 ± 3.35	78.20 ± 5.80
	FSCR (%)	52.17 (24/46)[a]	10.00 (1/10)[b]
	RB (%)	15.22 (7/46)	20.00 (2/10)
	SPC	1.98 ± 0.19[a]	2.90 ± 0.51[b]
	CCI (day)	109.96 ± 6.49	141.70 ± 14.76
	CR (%)	43.55 (27/62)	50.0 (6/12)
Overall		n = 425	n = 149
	DFS (day)	78.22 ± 1.39[a]	96.50 ± 3.15[b]
	FSCR (%)	40.06 (143/357)[a]	17.07 (21/123)[b]
	RB (%)	16.81 (60/357)[a]	30.08 (37/123)[b]
	SPC	2.24 ± 0.08[a]	2.91 ± 0.12[b]
	CCI (day)	121.82 ± 3.46[a]	165.09 ± 5.65[b]

DFS: Days to first service; FSCR: first service conception rate; RB: repeat breeder cows; SPC: service per conception; CCI: calving to conception interval; CR: culling rate.
[a,b]Values with different superscripts within rows differ (P < 0.05).

3.3.2. Exposure to postpartum heat stress

Heat stress did not affect the hazard of insemination (Fig. 4), DFS, FSCR, the proportion of breeders, SPC (Table 2), the hazard of conception (Fig. 5), CCI and CR (P > 0.05; Table 2).

3.4. Fertility during the third lactation

3.4.1. Maternal heat stress exposure

The hazard of insemination in the first trimester exposed cows was reduced compared with unexposed ones (AHR = 0.824; 95% CI = 0.684–0.993; P = 0.042; Fig. 2), but DFS did not differ between the first trimester exposed and unexposed cows (P > 0.05; Table 1). First service conception rate, the proportion of repeat breeders and SPC did not differ among various groups (P > 0.05; Table 1). The hazard of conception in the first trimester exposed cows was lower than unexposed ones (AHR = 0.799; 95% CI = 0.667–0.957; P = 0.015; Fig. 3), resulting in longer CCI in the first trimester exposed than unexposed cows (P = 0.019; Table 1). Culling rate in the second trimester exposed cows was higher than that in unexposed (AOR = 3.939; 95% CI = 1.312–11.827; P = 0.015) and the third trimester exposed (AOR = 4.274; 95% CI = 1.275–14.332; P = 0.019) cows (Table 1).

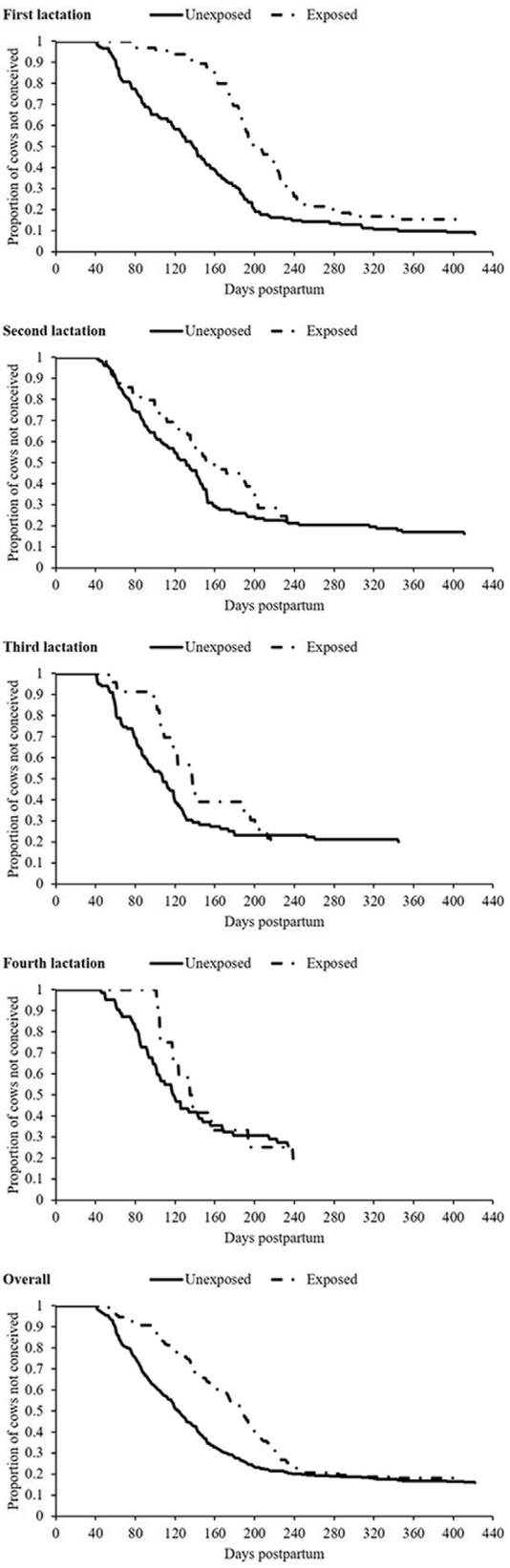

Fig. 5. Time to conception in female offspring unexposed and exposed to postpartum heat stress during the first, second, third and fourth periods of lactation, and overall.

3.4.2. Exposure to postpartum heat stress

The hazard of insemination was reduced in cows exposed to heat stress than unexposed ones (AHR = 0.551; 95% CI = 0.328–0.926; P = 0.025; Fig. 4), but DFS did not differ between two groups (P > 0.05; Table 2). First service conception rate was lower in heat stressed than unstressed cows (AOR = 0.303; 95% CI = 0.092–1.000; P = 0.050; Table 2). The proportion of repeat breeders was not different between two groups (P > 0.05; Table 2). Service per conception was higher in exposed than unexposed cows (P = 0.025; Table 2). The hazard of conception was reduced in exposed than unexposed cows (AHR = 0.516; 95% CI = 0.308–0.863; P = 0.012; Fig. 5), causing prolonged CCI in heat stressed than unstressed cows (P = 0.025; Table 2). Culling rate did not differ between two groups (P > 0.05; Table 2).

3.5. Fertility during the fourth lactation

3.5.1. Maternal heat stress exposure

The hazard of insemination in the first (AHR = 0.682; 95% CI = 0.513–0.907; P = 0.009) and second (AHR = 0.552; 95% CI = 0.352–0.868; P = 0.010) trimester exposed cows was reduced as compared with unexposed cows (Fig. 2), but DFS was not different among groups (P > 0.05; Table 1). First service conception rate, the proportion of repeat breeders and SPC did not differ among various groups (P > 0.05; Table 1). The hazard of conception in the first trimester exposed group was lower than unexposed group (AHR = 0.752; 95% CI = 0.577–0.978; P = 0.034; Fig. 3), causing longer CCI in first trimester exposed than unexposed cows (P = 0.030; Table 1). Culling rate was not different among groups (P > 0.05; Table 1).

3.5.2. Exposure to postpartum heat stress

The hazard of insemination (Fig. 4) and DFS (Table 2) did not differ between two groups (P > 0.05). First service conception rate was lower in exposed than unexposed cows (AOR = 0.104; 95% CI = 0.012–0.912; P = 0.041; Table 2). The proportion of repeat breeders did not differ between two groups (P > 0.05; Table 2). Service per conception was higher in exposed than unexposed cows (P = 0.034; Table 2). The hazard of conception was reduced in heat stressed than unstressed cows (AHR = 0.430; 95% CI = 0.203–0.912; P = 0.028; Fig. 5), but CCI did not differ between two groups (P > 0.05; Table 2). Culling rate did not differ between two groups (P > 0.05; Table 2).

3.6. Overall fertility

3.6.1. Maternal heat stress exposure

The hazard of insemination in the first (AHR = 0.790; 95% CI = 0.724–0.862; P < 0.0001), second (AHR = 0.585; 95% CI = 0.505–0.676; P < 0.0001) and third (AHR = 0.421; 95% CI = 0.317–0.560; P < 0.0001) trimester exposed cows was reduced as compared with unexposed ones (Fig. 2), which was reflected in DFS as well (P < 0.0001; Table 1). Moreover, the hazard of insemination in the second trimester exposed cows was lower than that in the first trimester exposed ones (AHR = 0.774; 95% CI = 0.602–0.995; P = 0.046; Fig. 2), resulting in longer DFS in the second than first trimester exposed cows (P = 0.002; Table 1). First service conception rate was lower in the third trimester exposed than unexposed cows (AOR = 0.460; 95% CI = 0.256–0.828; P = 0.010; Table 1). The proportion of repeat breeders in the first (AOR = 2.309; 95% CI = 1.135–4.696; P = 0.021), second (AOR = 2.442; 95% CI = 1.162–5.133; P = 0.019) and third (AOR = 3.061; 95% CI = 1.482–6.325; P = 0.003) trimester exposed cows was higher than unexposed ones (Table 1). Service per conception was higher in the second (P = 0.031) and third (P = 0.003) trimester exposed cows than unexposed ones (Table 1). The hazard of conception in the first (AHR = 0.862; 95% CI = 0.793–0.937; P = 0.001), second (AHR = 0.714; 95% CI = 0.622–0.819; P < 0.0001) and third (AHR = 0.546; 95% CI = 0.416–0.716; P < 0.0001) trimester exposed cows was reduced as compared with unexposed ones (Fig. 3), leading to longer CCI in the respective exposed groups than unexposed group (P < 0.001; Table 1). Furthermore, the hazard of conception was lower in the second than first trimester exposed cows (AHR = 0.753; 95% CI = 0.585–0.969; P = 0.028), causing prolonged CCI in the second trimester exposed cows as compared with the first trimester exposed ones (P = 0.038; Table 1).

3.6.2. Exposure to postpartum heat stress

The hazard of insemination was lower in heat stressed than unstressed cows (AHR = 0.540; 95% CI = 0.437–0.668; P < 0.0001; Fig. 4), culminating in longer DFS in exposed than unexposed cows (P < 0.0001; Table 2). First service conception rate was lower in exposed than unexposed cows (AOR = 0.303; 95% CI = 0.180–0.511; P < 0.0001; Table 2). The proportion of repeat breeders was higher in heat stress exposed than unexposed cows (AOR = 2.198; 95% CI = 1.352–3.572; P = 0.002; Table 2). Service per conception was higher in heat stressed than unstressed cows (P < 0.0001; Table 2). The hazard of conception was reduced in exposed than unexposed cows (AHR = 0.552; 95% CI = 0.448–0.682; P < 0.0001; Fig. 5), which was also reflected in CCI (P < 0.0001; Table 2).

3.7. AMH concentration

3.7.1. Maternal heat stress exposure

In the first lactation period, AMH concentrations were lower in the second trimester exposed than unexposed cows (P = 0.049; Table 3). In the second, third and fourth lactation periods, AMH did not differ among various groups (P > 0.05). Consolidating cows in different lactations, AMH concentrations were lower in the second (P = 0.0002) and third (P = 0.028) trimester exposed cows compared with unexposed ones; moreover, concentration of AMH in the second trimester cows was lower than that in the first trimester exposed ones (P = 0.001; Table 3).

3.7.2. Exposure to postpartum heat stress

Neither AMH concentration during the first, second, third and fourth lactation nor the overall AMH concentration regardless of lactation number were affected by exposure to heat stress at the time of blood sampling (P > 0.05; Table 4).

4. Discussion

The present study was conducted to investigate the effect of maternal exposure to heat stress on reproductive performance and AMH concentration, as a reliable marker of ovarian reserve [26,27], in the resultant female offspring in cattle. The results revealed that prenatal exposure to heat stress could delay first insemination postpartum, reduce fertility, prolong calving to conception interval and increase culling rate in the offspring. Additionally, prenatally heat stress exposed offspring had lower concentrations of AMH, implying that maternal exposure to heat stress during gestation could result in offspring with smaller size of ovarian reserve. To our knowledge, this is the first report in this regard.

Placenta is the only conduit supplying oxygen and nutrients to the fetus [34]. Heat stress has been observed to decrease placental weight [21], reduce total placental and umbilical blood flow [35], impair placental vascularization [35,36], increase placental resistance to oxygen, which hinders transplacental oxygen diffusion and

Table 3
Concentration of AMH (pg/ml) in female offspring considering exposure to heat stress during different stages of fetal development at the first, second, third and fourth lactation. Data are presented as mean ± SEM.

Parameter	Unexposed (n = 35)	First trimester exposed (n = 35)	Second trimester exposed (n = 38)	Third trimester exposed (n = 37)
First lactation	720.02 ± 95.72[a]	692.36 ± 106.71[ab]	355.26 ± 45.95[b]	489.54 ± 107.79[ab]
Second lactation	632.20 ± 87.12	652.16 ± 115.09	393.69 ± 82.13	380.02 ± 107.00
Third lactation	624.68 ± 156.29	572.90 ± 153.11	249.22 ± 45.64	394.53 ± 62.96
Fourth lactation	444.33 ± 55.08	409.65 ± 107.30	272.91 ± 67.38	388.20 ± 83.25
Overall	618.00 ± 52.82[a]	590.10 ± 60.38[ac]	320.13 ± 31.25[b]	415.09 ± 46.20[c]

[a,b,c]Values with different superscripts within rows differ (P < 0.05).

causes hypoxia [36], compromise transport of glucose through downregulation of glucose transporter in placental tissue [37] and impair transportation of amino acids [38]. Additionally, heat stress decreases dry matter intake in dam, which could exacerbate the condition [39]. Maternal undernutrition has been reported to diminish ovarian reserve in the offspring in bovine [11]. In ovine, maternal undernutrition could disturb fetal ovarian development [12,14], impair postnatal ovarian function [13] and disrupt the expression of genes regulating apoptosis in fetal ovary [14]. Moreover, maternal undernutrition has been observed to induce apoptosis in ovaries and to reduce ovarian vascularization in rat offspring [40]. Therefore, the potential disruption of placental function in response to maternal heat stress exposure could have led to fetal malnourishment, thus impairing fertility and ovarian reserve in the offspring.

Moreover, exposure to heat stress increase epinephrine and norepinephrine in cows [41,42]. The potential hypoxia induced by maternal heat stress could also elevate secretion of catecholamines in the fetus [43]. Suppressing insulin secretion, catecholamines favor the glucose uptake in insulin-independent over insulin-dependent tissues, including ovary [44], which would lead to asymmetrical intrauterine growth restriction [43]. In support of this, catecholamines have been indicated to abrogate follicular development and impair ovarian reserve via triggering apoptosis in rats [16]. Hence, the detrimental effect of prenatal heat stress on fertility and ovarian reserve in the present study might have been partly mediated through elevation of catecholamines.

Alternatively, heat stress has been indicated to result in oxidative stress in ovine [45,46] and porcine [47]. It seems that oxidative stress contributes to follicular apoptosis and atresia [48], and could compromise ovarian function [49]. Undernourishing rats during pregnancy and lactation, Bernal et al. [15] found elevated ovarian oxidative stress in concordance with depleted ovarian reserve. More recently, Xu et al. [50] indicated that the detrimental effect of maternal high fat diet during pregnancy on the ovarian function of offspring is regulated by oxidative stress promoting cell apoptosis in porcine. Nevertheless, the information is limited with regard to either the effect of heat stress on oxidative stress or the impact of prenatal oxidative stress on ovarian reserve and fertility of offspring in bovine, and it requires further research to be elucidated.

Further, the present study showed that with regard to reproductive system development, the susceptibility of bovine fetus to prenatal heat stress depends on the stage of pregnancy with the second and third trimesters of pregnancy_ particularly the second one_ as the most critical periods. Number of primordial follicles at birth is under the influence of various developmental processes taking place over the fetal period in bovine and human, including the number of primordial germ cells (PGCs) residing on the gonadal ridges, the rate of proliferation as well as apoptosis in PGCs from residence to cessation of mitosis, primordial follicles assembly, during which ovarian germ cell nests break down to form primordial follicles, and primordial to primary follicle transition [51,52]. In bovine, the migration and proliferation of PGCs, and the differentiation of PGCs to oogonia occur during the first trimester of gestation [53]; primordial follicles assembly initiates from the end of the first trimester [54] or the beginning of the second trimester [8,9] of gestation; and primordial to primary follicle transition commences from the second trimester of gestation [8,9]. Hence, insignificant effect of prenatal heat stress on AMH concentration implicates that perhaps PGCs and/or oogonia were more resistant to detrimental effects of maternal exposure to heat stress or the mitotic capability of oogonia helped compensate the imposed damage when the heat stress exposure terminated. On the other hand, lower AMH concentration in the second and third trimester exposed groups indicates that prenatal heat stress could diminish the absolute pool of primordial follicles in bovine offspring.

Any factor(s) abolishing the formation of primordial follicles and/or expediting the transition of primordial to primary follicles could cause depletion of ovarian reserve at birth [11,51], thereby adversely influencing the fertility of an individual for life [1–3]. As aforementioned, the potential undernutrition, elevation of catecholamines and/or oxidative stress induced by heat stress could have triggered apoptosis and depletion of primordial follicles. Regardless, steroid hormones, including estradiol, progesterone and testosterone, have been suggested as pivotal regulators of primordial follicles assembly and activation [9,54–57]. In this context, estradiol and progesterone regulate the formation of primordial follicles [9,54,58]. It is believed that the local synthesis of estradiol and progesterone by fetal ovary rather than maternal circulatory estradiol and progesterone contribute to primordial follicles assembly in bovine [54]; however, whether heat stress could influence the production of these steroids in fetal ovary is not known to our knowledge. Conversely, testosterone could stimulate follicle activation in fetal ovary in bovine [56] and human [59] in vitro. In ovine, maternal treatment with testosterone has been reported to decrease the number of primordial follicles through enhancing follicular activation [55,57]. Moreover, the diminishing effect of maternal nutritional restriction on the ovarian reserve of offspring has been attributed to resultant hyperandrogenemia in maternal circulation in bovine [11]. However, heat stress exposure during pregnancy in murine decreased the anogenital distance in male offspring, which implies lower fetal exposure to maternal testosterone during gestation [60]. Whether heat stress could influence maternal testosterone concentration in bovine requires to be addressed by further studies.

Table 4
Concentration of AMH (pg/ml) in female offspring considering heat stress exposure at the time of blood sampling. Data are presented as mean ± SEM.

Parameter	Unexposed (n = 104)	Exposed (n = 41)
First lactation	641.00 ± 60.11	479.96 ± 57.43
Second lactation	526.74 ± 64.71	803.91 ± 128.49
Third lactation	358.89 ± 40.43	224.99 ± 27.91
Fourth lactation	425.43 ± 71.42	402.92 ± 57.50
Overall	496.64 ± 31.21	442.82 ± 46.69

Yet it is notable that not all the effects of prenatal heat stress on reproduction could be attributed to diminished ovarian reserve. Since prenatal heat stress has been reported to impact the development of various organs including central nervous system [61,62], which plays a key role in regulation of reproductive system by secretion of gonadotropins [63]. There is also evidence that prenatal heat stress could alter the immune and metabolic function in the calf [22,23]. Whether these alterations extend for life in the offspring is unknown, but if so, it could impact the reproductive performance of cows, particularly during postpartum period [64,65].

In the present study, only prenatal heat stress during the third trimester of gestation decreased birth weight, which is consistent with previous studies in cattle [23,24]. It stems from the fact that most of fetal growth occurs during the last two month of pregnancy in bovine [66]; therefore, the first and second trimester of gestation might be of less significance as compared with the third one in this regard. Given the asymmetric development of various fetal organs during different stages of gestation [67], this phenomenon interestingly highlights that there might be various temporal patterns for the effect of prenatal heat stress with regard to different organs. Likewise, subjecting cows to restricted nutrition from 11 days before artificial insemination to day 110 of pregnancy, Mossa et al. [11] observed reduction of ovarian reserve but no change of birth weight in the offspring.

Finally, maternal chronic cold stress, causing sympathetic stress, has been recently reported to impair fertility of the second generation, which did not experience prenatal cold stress themselves but their mothers (the first generation) were exposed to prenatal cold stress [68]. In this context, prenatal paternal heat stress has been observed to alter DNA methylation and gene expression in the male offspring [69]. In addition, the effect of heat stress on alteration of DNA methylation in sperm [70], early developing embryo [71] and adult animal [72] has been reported. However, whether maternal heat stress exposure could influence the epigenetic of the female offspring and lead to transgenerational reproductive alterations is not known to our knowledge and warrants to be studied.

Regardless of the effect of prenatal heat stress, postpartum exposure to heat stress diminished reproductive performance in dairy cows in the present study, which agrees with previous findings [17,18,73]. The detrimental effect of heat stress on fertility of cows could be attributed to the adverse effect of heat stress on estrus detection [73], oocyte quality [19], embryonic development [20], progesterone concentration [18] and endometrial function [18].

5. Conclusion

Taken together, the present study showed that maternal heat stress could adversely impact fertility, productive longevity and ovarian reserve in the future generation. Moreover, the present study revealed that the second and third trimester of gestation might be more critical periods with regard to the influence of prenatal heat stress on reproductive performance and ovarian reserve in the female offspring. Indeed, the present study indicates that negative effects of heat stress are not limited to production and reproduction of lactating cows and could proceed to subsequent generation. These findings could help develop methods to alleviate the detrimental effects of heat stress in cattle. Further studies could decipher the downstream mechanisms whereby prenatal heat stress impairs fertility and ovarian reserve in the offspring.

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