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The effect of Seasonal heat stress on oxidants–antioxidants biomarkers, trace minerals and acute-phase response of peri-parturient Holstein Friesian cows supplemented with adequate minerals and vitamins with and without retained fetal membranes

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Abstract

Background: The global warming has become a worldwide problem affecting adversely the human being and the productivity of the livestock. This study aimed to investigate the effect of seasonal heat stress on the incidence of retained fetal membranes, oxidant-antioxidant biomarkers, haptoglobin, mineral status, milk production, inseminations/conception, estradiol, and days open of Holstein Friesian cows raised under Egyptian environmental conditions. Blood samples were collected one week before parturition and one day after parturition from two dairy farms. Total proteins, albumin, nitric oxide (NO), glutathione reduced (GSH), haptoglobin, estradiol, calcium, phosphorus, iron, copper and zinc were measured in the blood serum for cows delivered during the hot months (May to September) and the cold months (December to April).

Results: Cows delivered during the hot months had the highest prevalence of retained placenta and were older ($P=0.0001$) of mean parity (4.93 ± 2.24), required more services/conception ($P=0.0001$; 3.14 ± 1.20), produced higher ($P=0.0001$) milk yield/Ton (8.43 ± 1.29) compared to those retained during the cold months (8.00 ± 1.03). All cows retained their placentae had low estradiol ($P=0.0001$) compared to those dropped their placenta within the same season. All cows retained their fetal membranes had high NO ($P=0.0002$) but low GSH ($P=0.008$), and globulin ($P=0.041$). During the hot months, cows with retained placenta obtained low calcium, corrected calcium and calcium/phosphorus ratio. The type of placental drop and its interaction with season influenced ($P<0.01$) services / conception, milk yield, NO, estradiol and copper.

Conclusions: The retention of fetal membranes decreased the productive and reproductive parameters and its effects deteriorated reproduction and immunological status during the hot months.

Keywords: Cow productivity, Mineral status, Oxidant–antioxidants, Retained placenta, Season

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Background

The high producing dairy cows approaching calving are more subjected to metabolic fluctuations, negative energy balance, shortage of proteins, minerals, vitamins and antioxidants (Mordak et al. 2017). All cows experience a degree of reduced feed intake, negative energy balance, insulin resistance, hypocalcaemia and reduced immune function during the transition period. The various methods of clinical monitoring of health involving the level of milk production, feed intake, body condition scoring, reproductive health indicators, percentage of cases of retained placenta (RP) in the herd as well as different laboratory tests of blood and other samples, should be performed before and after calving (LeBlanc 2013). The retention of the fetal membranes is one of the common disorders in bovine causing economic losses (Laven and Peters 1996) due to the decrease in milk production, consumption of medications and the veterinary care to avoid the development of metritis and mastitis in complicated cases (Farzaneh et al. 2006; Stephen 2008). In dairy cows, the incidence of RP was 10%, and it is considered one of the main important health problems after mastitis and lameness on dairy farms (Suthar et al. 2013).

The causative factors of RP included age, breed, heredity, environment, season, gestation length, abnormal parturition, hormonal imbalance, nutrition and decreased neutrophil function (Han and Kim 2005; Kimura et al. 2002). Lowered levels of vitamins, minerals (Akar and Yeldiz 2005) and antioxidants (Kankofer 2001) caused RP. Inadequate supplementation of copper and zinc increased the incidence of RP (Markiewicz et al. 2001). In cows, lowered concentrations of iron (Sivaraman et al. 2003), calcium, phosphorus, zinc and copper (Sheetal et al. 2014) were related to retention of the fetal membranes. However, the pre-partum supplementation affected parturition and reduced placental expulsion period in dairy cows (Khanthusaeng et al. 2014).

This study aimed to evaluate the effect of season on the incidence, nutritional status, blood biochemical, oxidants–antioxidant biomarkers and acute-phase response of dairy cows supplemented with minerals and vitamins and delivered with or without retained fetal membranes.

Methods

Animals and management

Pregnant Holstein Friesian cows ($N=290$) of 3–10 years were kept in open semi-shaded yards and belonged to two private dairy herds at Shakia Governorate. Before conducting the study, the owners of the two dairy farms had permitted the blood sampling of cows. The study followed the international farm animal welfare regulations (Freedom from hunger and thirst, discomfort, pain; injury, and disease) and collected blood samples

according to the regulation of the National Research Center Animal and Use Care Committee. Cows were fed a properly formulated ration according to NRC (2001). Animals were subdivided into those gave normal birth during the cold months (December to April; $N=117$), those retained their fetal membranes during cold months ($N=6$), those gave normal birth during the hot months (May to September, $N=138$) and those retained their fetal membranes during hot months ($N=29$). Animals were supplemented with mineral mixtures and dewormed periodically. Cows encountered retained fetal membranes were treated appropriately. Subsequent milk yield was counted during the following 305 days. Data of services per conception and days open were also collected for all cows after pregnancy detection and confirmation. Cows were supplemented with mineral mixture at dose rate 10 gm/50 kg body weight and Vitamin AD3E at dose rate 5gm /50Kg body weight. Neither anesthesia nor euthanasia was applied.

Animals were handled according the Institutional animal care and use committee (IACAUC) of the National Research Center.

Blood samples

Blood samples were collected one week before calving and one day after calving from the tail vein in sterile blank blood collecting tubes. Sera were harvested and stored at -20°C after centrifugation at 3000 rpm for ten minutes.

Measurement of antioxidants, blood biochemicals, traces minerals and estradiol

Glutathione reduced (GSH), total proteins, albumin, nitric oxide, calcium, phosphorus, iron, zinc and copper were measured using commercial colorimetric kits (Bio-diagnostic, Egypt). The globulins were calculated by subtracting the concentration of albumin from those of the total proteins. Calcium/phosphorus ratio was counted by dividing the concentration of the calcium on the concentrations of the phosphorus. The corrected calcium concentrations were performed using the equation of Gild et al. (2015) where the estimated corrected calcium (mg/dl) = Measured Calcium (mg/dl) - Albumin (g/dl) + 3.5

Estradiol ELISA commercial kit was assayed (E2, DRG[®], EIA-2693) which has a sensitivity of 9.714 pg/mL, intra- and inter-assay precisions of 2.71 and 6.72%. Haptoglobin (BEN-BIOCHEMICAL ENTERPRISE S.r.l. - via Toselli, <https://www.ben-srl.com/>) was done by an immuno-turbidimetric method by mixing a sample with a precise antigen to a solution having the corresponding anti-serum (Antibody anti-Haptoglobin (goat) in PBS > 25 mmol/L NaN₃ < 0.1%) using Multipoint calibrators to prepare a Calibration Curve. The sensitivity limit

was 2.9 mg/dL. Within-run precision and Run to Run Precisions was 2.1%.

Statistical analysis

Data are presented as mean ± SD (Standard deviation) using SPSS 20 (2012). Simple one-way ANOVA was used to study the effect of season of birth with or without the retention of the fetal membranes on all the studied parameters. Duncan’s Multiple Range tests were performed to differentiate between significant means at $P < 0.05$. Multi-variate general linear model was used to study the effect of the placental drop (normal/retained), season (hot/cold), BCS ($> 3.5 / < 3.5$), the interaction of season with BCS, the interaction of season with placental drop, and the interaction of BCS with placental drop on the tested parameters.

Results

The results presented in Table 1 illustrate that the prevalence of retained fetal membranes was high during the hot months (17.37%) compared to the cold months

(4.88%). Cows retained their fetal membranes during hot months had the high milk production, required more services per conception and of high parity compared to the other cows delivered normally during the hot months. Cows retained their fetal membranes during the cold and the hot months had lower estradiol than cows delivered normally.

Cows with retained placenta during the hot months had higher total proteins ($P = 0.0001$), albumin ($P = 0.0001$), and albumin/globulin ratio ($P = 0.007$) but lower globulin ($P = 0.041$) than cows delivered normally. Cows delivered during the cold months with retained placenta showed a slight decrease in their total proteins and globulins with a slight increase in the albumin/globulin ratio (Table 2). Cows with retained placenta during both hot and cold seasons had higher nitric oxide ($P = 0.002$), but lower GSH ($P = 0.008$) than those delivered normally.

Regarding the mineral status of the cows presented in Table 3, cows had retained placenta during the hot months ($P = 0.001$) had the lowest zinc concentrations, calcium ($P = 0.015$), corrected calcium ($P = 0.0001$) and

Table 1 Mean ± SD of parity, milk yield/ton, services/conception, days open and estradiol in dairy cows calving during winter/heat stress with and without retained fetal membranes

Months Parameters	Cold		Hot		P value
	Normal	Retained	Normal	Retained	
Number of cows	117	6	138	29	
Number of samples	234	18	276	87	
Prevalence	95.12% ^d	4.88% ^a	82.26% ^c	17.37% ^b	0.0001
Milk yield/ton	7.87 ± 1.79 ^b	8.00 ± 1.03 ^b	6.87 ± 2.41 ^a	8.43 ± 1.29 ^b	0.0001
Parity	2.67 ± 1.49 ^a	3.00 ± 0.47 ^a	3.04 ± 1.63 ^a	4.93 ± 2.24 ^b	0.0001
Services/conception	1.35 ± .63 ^a	1.52 ± .51 ^{ab}	1.79 ± .80 ^b	3.14 ± 1.20 ^c	0.0001
Days open	65.66 ± 11.68	65.34 ± 5.41	69.35 ± 15.57	69.66 ± 18.95	NS
Estradiol pg/ml	982 ± 4.92 ^d	836 ± 16.06 ^a	953 ± 6.93 ^c	898 ± 9.81 ^b	0.0001

Means with different superscripts (a, b, c, d) are significant at $P < 0.05$, NS (non-significant)

Table 2 Mean ± SD of total proteins, albumin, albumin/globulin ratio, nitric oxide, glutathione reduced and haptoglobin in dairy cows during winter/heat stress with and without retained fetal membranes

Months Parameters	Cold		Hot		P value
	Normal	Retained	Normal	Retained	
Total proteins g/dl)	5.65 ± .07 ^b	5.46 ± .18 ^b	5.17 ± .07 ^a	5.52 ± .11 ^b	0.0001
Albumin (g/dl)	4.69 ± .06 ^b	4.68 ± .12 ^b	4.36 ± .088 ^a	4.79 ± .11 ^b	0.0001
Globulin (g/dl)	1.39 ± .06	1.17 ± .14	1.35 ± .08	1.18 ± .13	0.041
Albumin/globulin	3.70 ± .20 ^a	4.06 ± .45 ^{ab}	4.18 ± .37 ^{ab}	4.86 ± .62 ^b	0.007
NO (µmol/l)	26.83 ± 1.81 ^a	33.49 ± 5.80 ^b	24.63 ± 1.60 ^a	35.15 ± 2.46 ^b	0.002
GSH(g/dl)	32.11 ± 2.11 ^b	19.48 ± 7.12 ^a	24.75 ± 1.56 ^a	22.60 ± 2.92 ^a	0.008
Haptoglobin mg/dl)	14.86 ± 1.85	13.46 ± 4.98	14.16 ± 1.21	18.38 ± 1.78	NS

Means with different superscripts (a, b, c) are significant at $P < 0.05$, NS (non-significant), NO (nitric oxide), GSH (glutathione reduced)

Table 3 Mean \pm SD of zinc, copper, iron, calcium and phosphorus concentrations in dairy cows during winter/heat stress with and without retained fetal membranes

Months Parameters	Cold		Hot		P value
	Normal	Retained	Normal	Retained	
Zinc /ug/dl	222 \pm 2.92 ^b	218 \pm 2.42 ^{ab}	214 \pm 2.18 ^{ab}	213 \pm 2.20 ^a	0.001
Copper /ug/dl	210 \pm 5.75	223 \pm 8.56	227 \pm 6.76	229 \pm 4.72	0.08
Iron /ug/dl	209 \pm 10.12 ^a	201 \pm 16.79 ^a	246 \pm 13.29 ^b	249 \pm 13.29 ^b	0.007
Phosphorus	4.24 \pm .02 ^{bc}	4.29 \pm .07 ^b	4.15 \pm .02 ^a	4.22 \pm .04 ^{ab}	0.003
calcium	10.26 \pm .08 ^{ab}	10.27 \pm .24 ^{ab}	10.33 \pm .08 ^b	10.02 \pm .17 ^a	0.015
Corrected calcium	9.07 \pm 0.79 ^b	9.09 \pm 0.82 ^b	9.47 \pm 1.07 ^c	8.73 \pm 1.09 ^a	0.0001
Calcium/Phosphorus	2.57 \pm .02 ^{ab}	2.54 \pm .07 ^a	2.64 \pm .02 ^b	2.51 \pm .04 ^a	0.008

Means with different superscripts (a, b, c) are significant at $P < 0.05$

calcium/phosphorus ratio ($P = 0.008$), but the highest iron ($P = 0.007$), and copper ($P = 0.08$).

It is noticed from Table 4 that the type of placental drop influenced the services /conception ($P = 0.004$), milk yield ($P = 0.017$), globulin ($P = 0.015$), albumin/globulin ratio ($P = 0.047$), NO ($P = 0.079$), estradiol ($P = 0.0001$) and copper ($P = 0.045$). Season influenced services /conception ($P = 0.0001$), Days open ($P = 0.017$), milk yield ($P = 0.002$), NO ($P = 0.0001$), haptoglobin ($P = 0.002$), estradiol ($P = 0.020$), iron ($P = 0.0001$) and copper ($P = 0.004$). BCS significantly affected services /conception ($P = 0.0001$), Days open ($P = 0.006$), total proteins ($P = 0.003$), globulin ($P = 0.008$), albumin/globulin ratio ($P = 0.005$), GSH ($P = 0.022$) and estradiol ($P = 0.045$). The interaction of season with the type of placental drop had significant effects on services /conception ($P = 0.0001$), milk yield ($P = 0.005$), GSH ($P = 0.010$), NO

($P = 0.0001$), E2 ($P = 0.0001$) and phosphorus ($P = 0.004$), but tended to influence total proteins ($P = 0.068$), iron ($P = 0.091$) and copper ($P = 0.086$). The interaction of type of placental drop with BCS influenced services /conception, days open, NO ($P = 0.0001$), milk yield ($P = 0.002$), total proteins ($P = 0.003$), GSH ($P = 0.010$) and phosphorus ($P = 0.004$), but tended to influence iron ($P = 0.091$). The interaction of season with BCS affected milk yield and estradiol ($P = 0.0001$), but tended to influence iron ($P = 0.091$).

Discussion

Retained placenta is a common disorder affecting high producing cows (Stephen 2008; Sheetal et al. 2014). The current work revealed lower incidence of retained placenta during the cold months (7.14%) which increased markedly > three times during the hot months (23.79%)

Table 4 The effects of season, BCS, Type of placental drop and their interactions on productive and reproductive parameters

Dependent variable	Corrected model	Placental drop	Season	BCS	Placental * Season	Season * BCS	Placental * BCS
Services/conception	0.000	0.004	0.0001	0.0001	0.0001	0.618	0.0001
Days open	0.000	0.404	0.017	0.006	0.783	0.686	0.0001
Milk yield	0.000	0.001	0.002	0.241	0.005	0.0001	0.002
Total proteins	0.000	0.138	0.410	0.003	0.068	0.269	0.003
Globulin	0.004	0.015	0.545	0.008	0.290	0.975	0.117
Albumin/Globulin	0.042	0.047	0.673	0.005	0.788	0.856	0.797
NO	0.000	0.079	0.0001	0.311	0.0001	0.285	0.0001
GSH	0.000	0.402	0.572	0.022	0.010	0.518	0.010
Haptoglobin	0.000	0.884	0.002	0.670	0.215	0.468	0.649
Estradiol	0.000	0.000	0.020	0.045	0.0001	0.0001	0.822
Phosphorus	0.005	0.561	0.475	0.355	0.004	0.078	0.004
Iron	0.000	0.245	0.0001	0.656	0.091	0.448	0.091
Copper	0.000	0.045	0.004	0.443	0.086	0.976	0.678

and included older cows in their 5th parity. Similarly, the prevalence of retained placenta ascended linearly from 13.56 for cows at their first parity to 24% at \geq the fourth parity (Han and Kim 2005). Our incidence of cows with retained placenta during cold months agrees with the reported average of 5 to 10% under normal conditions in a dairy herd (Stephen 2008). Whereas, the increased prevalence of RP during the hot months is in agreement with increased percentage of cows with RP during the hot months from June to November (20.3%) compared to cold months from December to May (16.1%; Han and Kim 2005). In agreement with the increased incidence of RP during the hot months in older cows in their fifth parity, parity at the fifth calving had the maximum incidence of RP (Choudhury et al. 1993). Moreover, hormonal imbalance, age and season were the predisposing factors of RP (Han and Kim 2005; Kimura et al. 2002). In contrast to the observed increased milk production along the milk season following retained placenta, cows with RP following dystocia produced less milk with decreased food consumption (Newby et al. 2010). The increased incidence of RP during the hot months was referred the increased concentration of adrenaline by stimulating the myometrial adrenoreceptors causes hypotony or atony of the uterus and dystocia (Lamp et al. 2015).

This study found no changes in the zinc concentrations within the same season between cows with and without retained placenta (RP) but reported a significant decrease in calcium, corrected calcium and calcium/phosphorus ration in cows with retained fetal membranes during the hot months. As well as, lower values of serum calcium, phosphorus, zinc, copper and iron were reported in cattle (Hashem and Amer 2008; Sheetal et al. 2014) with retained placenta. Similarly, lower Ca and Zn levels were observed in cows with retained placenta which predisposed the development of placental retention (Akar and Yildiz 2005), and this decrease in calcium was referred to the excessive mobilization of calcium to the fetus during the last stages of pregnancy resulting in less availability to uterine tissue (Ke et al. 1994). Inadequate calcium concentrations predisposed to retained placenta (Hashem and Amer 2008; McDowell 1992; Zhang et al. 1992). The non-change in calcium levels during cold months associated with the decreased incidence of RP may be related to the including a good quality green clover rich in calcium in the ration of dairy cows during their dry period during the cold months and indicated no role of calcium in the development of RP when its levels were present within the physiological levels (Lotthammer 1983; Mutiga et al. 1993). In agreement with the decrease in total calcium levels during retained placenta, this decrease in corrected calcium was used as

a marker of hypoalbuminemia (Melendez et al. 2004). Moreover, hypocalcaemia with a calcium serum concentration was often observed with decreased serum phosphorus and zinc concentration in cows with RP (Moretti et al. 2015). Because cows with RP often have lower serum levels of calcium, magnesium and other elements in comparison with healthy cows, they should receive adequate supplementation in diet (Mee 2004). The inadequate vitamins and minerals in the diet normal limit their concentrations in the blood, inducing oxidative stress and immune suppression (Kendall and Bone 2006).

Similar to the association of RP of metabolic origin with decreased concentrations of minerals, mainly calcium, magnesium and total antioxidants indicating chronic hepatic damage (Bionaz et al. 2007), the interaction of BCS with RP of dairy cows of the current study indicated significant effects on total proteins, NO, GSH and phosphorus. The increased total proteins, albumin and albumin/globulin ratio in cows with retained placenta during the hot months and the same values during cold months are indicators of the good management of cows agreed with the associated insignificant change or slight increase in albumin with increased conception rate and longer days open one week before and after birth in cows with or without retained fetal membranes (Nogalski et al. 2012). Haptoglobin as a non-specific but important marker used for monitoring the calving time, did not increase in cows with retained placenta during cold months but increased slightly during the hot months and was associated with increased total proteins, albumin and decreased globulins that indicates the favorable responses of cows with RP to the treatment that was contradict with the significant increase in fibrinogen associated with low albumin and high globulins including fibrinogen and related to the inflammatory processes during placental retention in cows (Stockham and Scott 2002). In a similar manner, cows with RP following dystocia (Newby et al. 2010) or encountered acute puerperal metritis after the RP (Mordak 2009) obtained higher serum haptoglobin levels compared to animals without RP. The significant increase in albumin during the hot months in the cows with RP of this study indicated the absence of any inflammations or complications following appropriate treatment because albumin is one of the negative acute-phase proteins and its concentrations was decreased during acute inflammations and in RP cows (Stockham and Scott 2002). In another study, the periparturient metabolic stress indicated by elevated concentration of β -hydroxybutyrate (BHB) was associated with elevated serum haptoglobin and primiparous cows got higher serum haptoglobin concentration than multiparous cows 5 days postpartum but the elevated NEFA

2 days postpartum was not a risk factor for elevated Hp (Pohl et al. 2015).

Similar to the decreased estradiol concentrations in cows with RP during the cold and the hot months, low estradiol (Hashem and Amer 2008), estrogen (Farzaneh et al. 2006) and total estrogen (Hartmann et al. 2013) were noted pre- and postpartum cows in cows with RP. This decrease in estradiol in cows with RP was referred to the presence of immature placentomes (Hashem and Amer 2008). The decreased production of estrogen was referred to the imbalance of the placental antioxidant enzyme production which led to the decreased PGF_{2α} production and accumulation of arachidonic and linoleic acids within placental tissue (Wischrall et al. 2001). In contrast, a non-significant increase in estradiol (Kaczmarowski et al. 2006), and no change in estrone sulfate concentrations (Shah et al. 2007) was noted in dairy cows with retained fetal membranes.

In agreement with the current results, low GSH concentrations were observed in the cows (Kankofer 2001) with retained fetal membranes which resulted from the decreased antioxidant enzyme capacity of the placenta during pregnancy (Gupta et al. 2005; Wischrall et al. 2001). The increased NO levels during both seasons in cows with RP may refer to the important role of nitric oxide as a powerful smooth muscle relaxant capable of relaxing the myometrium during pregnancy and may be responsible for uterine quiescence (Sladek et al. 1997; Norman 1996; Yallampalli et al. 1993). The increased content of NO in buffalo, and cows with retained placenta was referred to its role in inhibiting uterine contraction as indicated by the over expression of iNOS protein and iNOS mRNA (Shixin et al. 2011). Superoxide dismutase may be important in governing the activity of nitric oxide within the uterus at the time of parturition. Superoxide dismutase is responsible for scavenging superoxide anions and hence prolongs the biological effects of nitric oxide. At the onset of parturition, a decrease in the activity of superoxide dismutase would reduce the availability of nitric oxide within the uterus and lead to an increase in uterine contractility. Xanthine oxidase, the enzyme responsible for superoxide synthesis, may attenuate the biological activity of nitric oxide as superoxide anion combines with nitric oxide to form peroxynitrite (Ledingham et al. 2000).

Conclusions

The heat stress has a detrimental effect on the prevalence of the retained placenta of older cows with high milk production. The supplementation of minerals and vitamin with adequate treatment improved the fertility and the productivity of retained animals regardless the increased services required for conception. Peripartum lowered

estradiol, corrected calcium and calcium phosphorus ratio with high nitric oxide may predispose to the retention of fetal membranes.

Abbreviations

BHB: β-Hydroxybutyrate; BCS: Body condition score; GSH: Glutathione reduced; iNOS: Intrinsic nitric oxide synthetase; mRNA: Messenger ribonucleic acid; NO: Nitric oxide; NEFA: Non-estratified fatty acids; P: Probability; PGF_{2α}: Prostaglandin F_{2α}; RP: Retained placenta.

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Authors' contributions

AM put the design, helped in the clinical analysis, performed statistical analysis and revised and submitted the manuscript. MAA helped in blood sampling and data collection, helped in the clinical analysis, and helped in writing the manuscript. MS helped in the clinical analysis and the statistical analysis. MAE helped in collection of blood and data, statistical analysis and writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Any required data will be available upon request from the corresponding author.

Ethics approval and consent to participate

The authors followed the international regulations of the farm animals' welfare and the regulations of the National Research Center Animal Care and Use Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they do not have any competing interests.

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