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A comprehensive survey on the effects of aflatoxin B1 in birth outcomes and milk yield of pregnant cows and buffaloes.

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Aflatoxins, highly toxic compounds produced by species of Aspergillus Flavus and Aspergillus parasiticus, are known carcinogens that are also associated with adverse birth outcomes. There are no published randomized controlled trials evaluating the effect of aflatoxin exposure during pregnancy. Therefore, we aimed to conduct a research investigate the potential role of aflatoxin exposure in intrauterine growth retardation, preterm birth, and pregnancy loss. This study was carried out on 1.600 pregnant animals (850 cows and 750 buffaloes) from different farms in three provinces during three years from (2017-2019). The results revealed that adverse birth outcomes due to aflatoxin exposure in pregnant cows and buffaloes are abortions, stillbirth and fetal resorption. Examination of the placenta of aborted cases and stillbirth indicate the presence of placental retention in addition to a leathery thickening of areas in between the cotyledons. Some cases of abortion and stillbirth have rectal prolapse but cases of fetal resorption do not have this problem, in the same time all cases have decreased milk yield. Studying the relationship among aflatoxin of diet with milk in both groups A and B revealed the presence of significant relationship ($P<0.05$) between total aflatoxin level in ration and aflatoxin levels in milk (M1) in all cases of abortion, stillbirth with low birth weight and fetal resorption in group B. Regarding to milk yield, there was no significant relationship between aflatoxin levels of feed and/or milk with milk production, somatic cell count, milk protein and fat.

Keywords: Aflatoxin B1, Birth outcomes, Aflatoxin M1, Buffaloes.

INTRODUCTION

Reproduction is vital for the continuation of all life species thus in medical, veterinary and biological sciences, reproduction is of authentic importance. Researches of animal and veterinary sciences, are mainly concentrated on factors which have a bad effect on reproduction and have an impact on economic loss(Hasanzadeh and Amani 2013). Mycotoxins are one of these factors which are produced by fungi with varied toxic potencies. Aflatoxin B1is one of the mycotoxins and is considered as the most toxic one commonly found in plant food(Leung et al., 2016).

Aflatoxins enter the body directly through consumption of contaminated food. These toxins have the ability to resist heat and light. After entering the body, they destroy different organs such as gonads. clinical symptoms of aflatoxicosis appear on the animal after entry of aflatoxin into the body, therefore two types of aflatoxicosis are present, i.e. acute aflatoxicosis which causes liver damage, thus disease and death, whereas chronic aflatoxicosis which result in nutritional(Ibeh et al. 1994), immunological and other minor pathologic anomalies(Faridha et al., 2007; Sur and Celik 2003).

But it is noticed that a lot of previous researches have focused on the destroying effect of these toxins on different body systems while very little number directed to the reproductive system and even those of reproductive system also restricted to the male system. Presence of aflatoxin in feed and exceeds its limit more than the critical level (20 in diet and 0.5µg/kg in milk) leads to low down fertility rate and reproductive ability in animals (Kabak et al., 2006; Zheng et al., 2005), delay in genital system growth(Hafez AH 1982), abortion(Ray et al., 1986), lowering pregnancy rate and number of live new born and death of the fetus intrauterine.

The role of most toxins on birth outcomes remains largely unknown. When pregnant mother ingest food or drink water contaminated by environmental toxins, the toxin reaches to the fetus. Aflatoxins are one of such toxins which can enter the mother body by the route of ingestion. Intrauterine growth retardation and low birth weight of the fetus are the biochemical, immunological and metabolic derangement caused by aflatoxins when reach to the fetus (Abdulrazzaq et al., 2004). It has been documented that long-term ingestion of aflatoxins in feed has carcinogenic, immunosuppressive and growth retarding effect (Fung and Clark 2004). However, very little number of studies has been done to detect the association of birth outcomes with aflatoxins but they have not shown specific outcomes. Therefore the following study was designed to investigate the deleterious effects of AFB1 on the birth outcomes of female buffaloes. It will be very useful also for the development of the productive and economic sector. Likewise, there is great relevance for animal and human health, as they may be contained as residues in dairy products.

MATERIALS AND METHODS

All procedures were approved and done according to the guide approved by the Ethics Committee of the Faculty of Veterinary Medicine, Aswan University, Egypt. This study was carried out on local breed pregnant cows and buffaloes in Aswan, Luxor and Qena provinces in Egypt during the period of three years from 2017 till 2019.

Study design

This study was carried out on 1.600 pregnant animals (850 cows and 750 buffaloes) from different farms in the three provinces. Animals were divided into two groups (A and B). Animals fed on ration stored of relatively high moisture and temperature (40^{O} c) but are very persistent under extreme environmental conditions.

The two groups were selected according to dietary aflatoxin level in milk production cows and buffaloes, group A (N=600): low aflatoxin level (with average 15.02µg/kg) which is lower than the standard level (20 µg /kg) and group B (N=1000): high aflatoxin level (with average 120.65µg/kg) which is higher than the standard level (20 µg /kg). Feeding and management conditions were the same for the whole herds.

The resident veterinarian of the farms carried examination for the two groups for detection of any reproduction problems such as(Pregnancy conditions, Retained placenta, Stillbirth and Fetal Resorption) and any other general symptoms during 50 to 100 days out pre and postpartum . Milk examinations include detection of milk production and composition which were carried out during 100 days postpartum.

Aflatoxin detection in feed and milk

HPLC system (Perkin Elmer model) was used to determine the amount of aflatoxin in ration and milk (M1) according to methods of Charoenpornsook and Kavisarasai (Charoenpornsook and Kavisarasai 2006) and Rosi (Rosi et al., 2007), respectively.

Statistical analysis

Statistical analysis was done by using SPSS Software (SPSS 20, IL, USA).Differences in means were analyzed using Student's t test for comparison between two groups. The data were presented as means and standard errors of means. The P value was considered significant if it was less than 0.05.

RESULTS

Table 1 shows the levels of aflatoxin in the ration. As shown in the table; feed content of aflatoxin in group B was evidently greater than group A (120.65 Vs. 15.02 µg/kg) which is more than six times the standard level (20 µg /kg).

Group B suffer from the symptoms of aflatoxin poisoning such as feed refusal, diminished milk yield and decreased feed efficiency. In addition, laziness, weight loss, roughness of hair coat and mild diarrhea with rectal prolapse may occur.

Anemia along with contusion and subcutaneous hemorrhage are also present.

Table 1: Aflatoxin levels (µg/kg) on ingredients of diet.

Parameters	Group A	Group B
Yellow corn	4.41	20.15
Soya bean	10.55	70.5
Wheat bran	0.32	0.95
Premix	0.23	0.88
Dicalcium phosphate	0.12	0.44

Table 2: Incidence rate of birth outcomes problems due to aflatoxin.

Item	Group A (n=1000)		Group B (n=1000)	
	Number	%	Number	%
Abortion	48	8	280	28
Stillbirth	0	0	320	32
Low Birth weight	456	76	320	32
Fetal Resorption	96	16	400	40
Retained placenta	48	8	600	60
Leathery thickening of placenta	48	8	600	60
Rectal prolapse	0	0	600	60
Decreased Milk production	360	60	1000	100

Table 2 shows the incidence of birth outcome problems due to aflatoxin and indicate that pregnant cows suffer from abortions were about 28% and stillbirth 32% with low birth weight while fetal resorption was 40% in group B, on the same time there was no incidence of stillbirth in group A but there was 48 cases of abortion which represents (8%) and 96 cases of fetal resorption (16 %) while the rest of the group born alive but with low birth weight 76% (Fig.1).

Placenta of the cases of abortion and stillbirth has retention in group B(N=600) and is seen as a leathery thickening of areas in between the cotyledons while in group A ,only the cases of abortion has retention of placenta with leathery thickening.

Some cases in group B include abortion and stillbirth have rectal prolapse (N=600) but cases of fetal resorption did not have this problem, in the same time all cases have decreased milk yield while in group A, rectal prolapse did not occur and only 60 % of cases have decreased milk production.

Table 3: displays the relationship among aflatoxin of diet with milk in both groups A and B. It is noticed the presence of significant relationship ($P<0.05$) between total aflatoxin level in ration and aflatoxin levels in milk (M1) in all cases of abortion, stillbirth with low birth weight and fetal resorption in group B (Fig.3). In group A, it was found that there was no relationship between total aflatoxin level in ration and aflatoxin levels in milk (M1) in cases of abortion and fetal resorption but there was a significant relation between aflatoxin effect and low birth weight (Fig.2).

Regarding to milk yield, in both groups, milk production were detected during 100 days and so, there was no significant relationship between aflatoxin levels of feed and/or milk with milk production, somatic cell count, milk protein and fat.

Table 3: The correlation between aflatoxin and birth outcomes in cows and buffaloes.

Item	Group A		Group B	
	Diet(total)(µg/kg)	Milk(total)(ppb)	Diet(total)(µg/kg)	Milk(total)(ppb)
Abortion	10.26±0.02	0.04± 0.05	119.89±0.02*	0.53±0.01*
Stillbirth	------------	------------	115.20±0.03*	0.44±0.05*
Low Birth weight	7.52±0.02*	0.03± 0.07*	115.20±0.03*	0.44±0.05*
Fetal Resorption	9.56±0.03	0.05± 0.03	109.98±0.05*	0.36±0.04*

- Values are (mean ± SE).
- Means carrying superscripts are significantly different at (p-value<0.05).

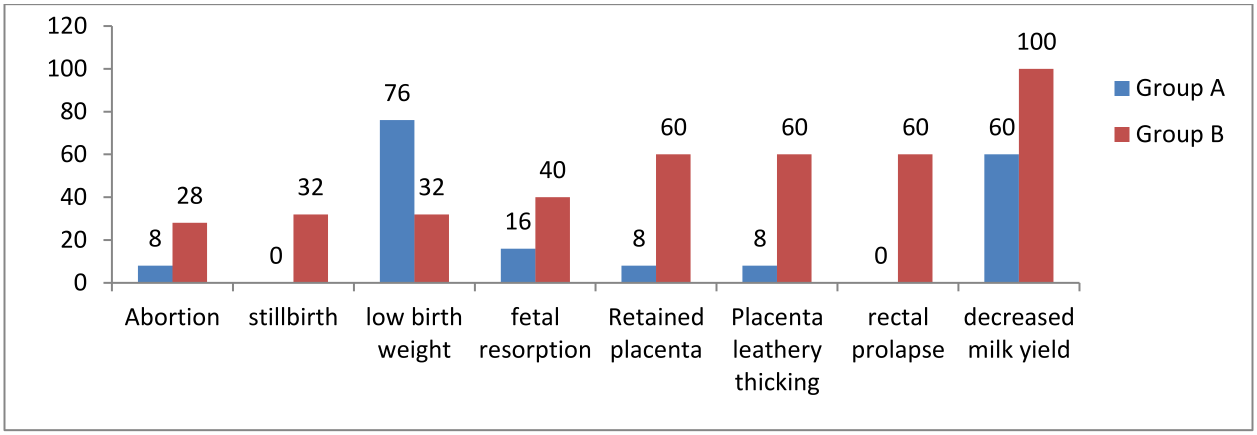

Figure 1: The incidence of birth outcome problems due to aflatoxin. Values are in the form of %.

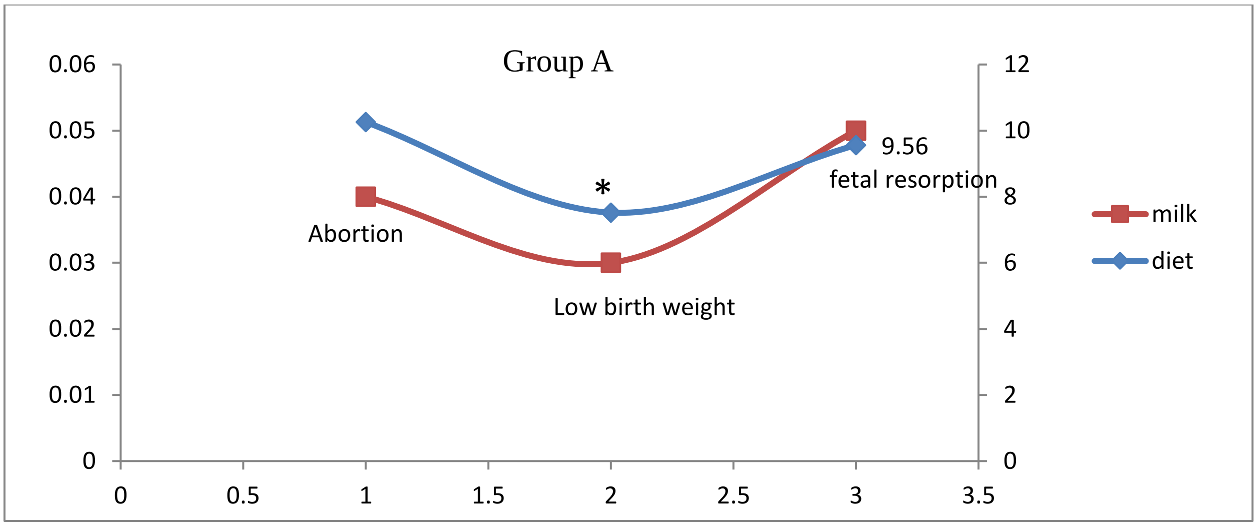

Figure 2: The correlation between aflatoxin and birth outcomes in cows and buffaloes in Group A.

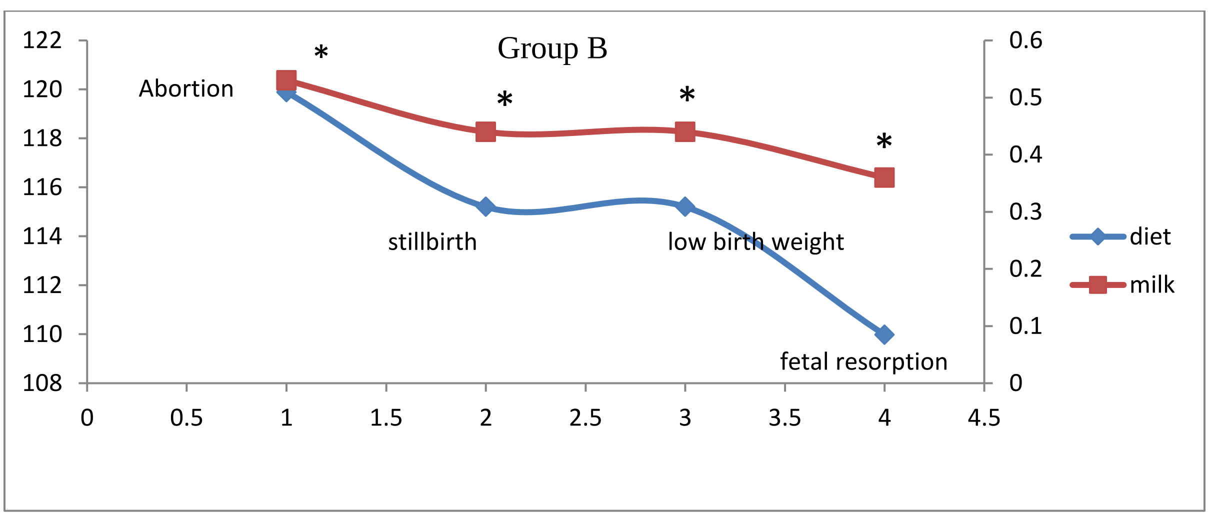

Figure 3: The correlation between aflatoxin and birth outcomes in cows and buffaloes in Group B.

DISCUSSION

food stuffs is contaminated by AFB1 in variant regions of the world such as the Middle East, China, India, Sub-Sahara in Africa and USA and this cause a huge problem (Williams et al. 2004).A significant relationship was presented between milk and dietary aflatoxin (Table 3).The high level of aflatoxin M1 in the milk resulted from the high level of aflatoxin in the ration so dietary aflatoxin such as metabolite of aflatoxin B1,was the source of aflatoxin of milk.

This result is in agreement with that of (Pirestani and Toghyani 2010) who reported that the ratio of milk aflatoxin(M1) has a significant relationship with the different kinds of aflatoxin such as G1 and /or B1 and the total aflatoxin levels, while only about 2.2% aflatoxin B1 in ration converted to aflatoxin M1(Lanyasunya et al., 2005; Özsoy et al., 2005).

The most common signs of toxicity with aflatoxin in buffaloes were feed refusal, decreased milk production and decreased feed efficiency , laziness, weight loss, rough hair coat and mild diarrhea. These symptoms are similar to that found by(Eaton 1994; Ray et al., 1986) who noticed that acute toxicosis in cattle include loss of appetite, bleakness, great decrease in milk yield, decrease weight, lethargy, ascites, jaundice, tenesmus, pain in abdomen , bloody diarrhea, hepatoencephalopathy, photosensitization and bleeding. This Decreased performance of toxicated buffaloes (i.e. rate of gain, milk production) is likely caused due to several factors, including not only nutritional interactions, but also the accumulated effects of appetite loss, deranged hepatic protein, lipid metabolism and disorder in hormonal metabolism(Raisbeck et al. 1991). Aflatoxins also cause decreasing in cellulose digestion, volatile fatty acid production and proteolysis (Bodine and Mertens 1983) therefore it has been known that aflatoxin affect in rumen motility (Cook et al., 1986) and rumen function.

Pregnant and growing animals are more susceptible to aflatoxicosis than mature animals but less susceptible than young animals (Cassel et al., 1988). One of the most important signs of aflatoxicosis is abortion which occur in 28% of group B and about 8% in group A and it is obvious that its low incidence in group A as it fed in ration contains low level of aflatoxin compared to group B. This gives an explanation to the significant relationship between the amount of aflatoxin in ration and the incidence of abortion.

Similar results were reported by(Eaton 1994) who observed that acute toxicosis in cattle cause abortion, ascites and icterus. Also (Ray et al., 1986) reported that feeding a herd of 68 crossbred cows in their third-trimester fetuses on moldy peanuts for 4 days lead to abortion in 12 % of the herd. Biochemical analysis of serum was carried out to the aborted cows and showed that liver damage occurred to these cows which then died within 8 days of abortion. Liquid chromatography was used to measure the content of peanut from aflatoxin which was 77 micrograms aflatoxin B1/g. One cow was chosen for submission of its tissues which indicate that liver contained 5 Nano gram aflatoxin B1/g.

The same reported by (Raisbeck et al., 1991) who said that disturbance of reproductive performance occur as a result of chronic aflatoxicosis such as loss of pregnancy by abortion and abnormal estrous cycle (too short and too long) plus its bad effects in immune system which include induction of immunosuppression and increase susceptibility to disease (Cassel et al., 1988). It was noticed also that AFB1 used cell-mediated immune system to express its immunotoxic effect. Also, other research carried out by (Ibeh et al., 1994) showed that aflatoxin B has deleterious effect on gonads, as it decrease the size of both ovaries and uterus, cause death of the embryos and decrease rate of pregnancy and birth.

(Leung et al. 2016) noticed that mice treated with aflatoxin B1suffered from increased incidence of preterm birth. Pregnant mice were used to isolate placental tissue to examine both the expression of the mRNA of CRH and to examine the two types of protein (pks and Bcl-2) in the aflatoxin treatment group. MRNA of CRH was found unregulated and this might signify premature delivery. For protein, Pkc was found activated and Bcl-2 was found reduced. On the other hand, morphorgenesis and maintenance of the placenta might be affected by the reduction on the anti-apoptotic proteins.

It is also noticed that mice treated with high doses of toxin has high concentration of CRH, estrogen and progesterone. Many hormones are secreted from the placenta during the course of pregnancy such as CRH which increases progressively as parturition approach. This increase in CRH make CRH bind to its receptor and leads to activation of Gs protein/CAMP signaling (Behan et al. 1995; Petraglia et al. 1989) subsequently triggers the cellular events leading to parturition.(McLean et al., 1995; Wadhwa et al., 1998).

The cause of preterm birth due to aflatoxin can be explained by knowing the mechanism of surge CRH release. Release of surge CRH coincides with the time of delivery whether premature, full-term or post-term is. Aflatoxin B1 make up-regulation of the CRH mRNA and subsequently increase plasma CRH concentration(Tuckerman et al., 2004).

Estrogen also plays a role in maintenance of pregnancy and parturition. In early pregnancy, if plasma estrogen levels were low, this is often accompanied by miscarriages(Tuckerman et al., 2004).During the transition from early pregnancy to labor, estrogen increased to promote myometrium development(Kilarski et al., 1993). Some studies indicated that the concentrations of 17-estradiol increased rapidly in both maternal plasma and amniotic fluid before the occurrence of preterm labor (Moore 1999; TambyRaja and Lun 1978).It was found that high level of aflatoxin B1 increased the plasma concentrations of estrogen in pregnant mice (Wang et al., 2016) leading to preterm labor.

In the current study, the stillbirth was found on group B that fed ration contain high level of aflatoxin compared to its absence in group A that fed ration has low level of aflatoxin . Also there is a significant relationship between total aflatoxin level in ration and aflatoxin levels in milk in cases of stillbirth in group B. These data strongly suggest that the aflatoxin caused the incidence of stillborn in pregnant buffaloes. Until today, very little number of reports not more than two reports considered the possible presence of relation between stillbirth and aflatoxin: high aflatoxin levels were reported by these two reports to be present in both maternal peripheral blood and cord blood(VRIES et al., 1989). Similarly, one stillbirth was reported by(Lamplugh et al., 1988)in their study, which was based on aflatoxin in maternal blood. (Diaz-Llano 2007) indicated that the feeding of contaminated grains with mycotoxins to sows in late gestation resulted in increased frequency of stillborn piglets, and supplementation with GMA prevented this effect. Other studies use different types of toxins carried out by(Miller et al., 1973) reported that feeding gilts a gestation diet containing 50 to 75 pg. of Zearalenone per 100 g of feed lead to incidence of stillbirth, splay leg and weak newborn piglet syndrome. These findings adverse with that detected by (Pirestani and Toghyani 2010) who reported that incidence of stillbirth, uterine infections and irregular estrus has no relation with the aflatoxin of milk and diet. Also(Shuaib et al., 2010) carried out a study and denied the presence of association between stillbirth and aflatoxins. He thought that stillbirth to occur due to aflatoxin will require much higher doses and longer duration of exposure to that toxin at critical periods of fetal life. Other studies use different types of toxins carried out by (Chavez 1984), showed that feeding of 3.3 mg Deoxynivalenol /kg to gilts during gestation did not have effects on reproduction.

There was no consensus on findings regarding the relationship between aflatoxins and birth weight. In the present study, there was a significant relationship between aflatoxin level in milk and fetuses born with low birth weight in both groups. This result corroborate other four studies (Abdulrazzaq et al., 2002; Abdulrazzaq et al., 2004; Abulu et al., 1998; Turner et al., 2007) who reported a negative correlation between birth weight and aflatoxin levels (with P values ranging from <0.001 to <0.05),while one study found no association between birth weight and aflatoxins in serum (Maxwell et al., 1994).Furthermore, one study reported that a significant association (P<0.01) between height at birth and aflatoxins(Sadeghi et al., 2009).This effect of aflatoxin in birth weight can interpreted by the theory that aflatoxin reach the fetal circulation after pass through the foeto-uterine barrier to do their variant heinous effects (Ibeh et al., 2000).

The effect of aflatoxin in early pregnant female buffaloes appear in the occurrence of fetal resorption which has a significant relationship with the level of aflatoxin in ration and subsequently in milk in group A and B. this result is in accordance with previous investigations worked by (Ibeh and Saxena 1997a; Ibeh and Saxena 1997b) who show that the effect of aflatoxin in reproductive health include increases in fetal resorption, implantation loss and intrauterine death in aflatoxin-exposed female rats

The results indicated that aflatoxin is responsible for occurrence of retained placenta in all the cases of abortion and stillbirth in group B and in the two cases of abortion in group A. The placenta characterized by leathery thickening in both groups. This results is similar to (Pirestani and Toghyani 2010) who reported that there is a significant relationship between aflatoxin M1, G1 and G2 with retained placental in dairy farm fed in ration has high level of aflatoxin.

In our study, aflatoxin affects in the rectum and caused its prolapse especially in group B in cases of abortion and stillbirth while in group A this did not happen. The same result found by

(Blood 2000; Guthrie and Bedell 1979) who reported that acute aflatoxicosis cause rectal prolapse, loss of vision, walking in circles, ear twitching, frothy at the mouth and kerato conjunctivitis.

In the current study, the results indicate that milk production also affected by ingestion of aflatoxin by reducing its amount. This finding is similar to that found by(Guthrie and Bedell 1979) who shown that aflatoxicosis in chronically exposed cattle causes reduction in milk yield, acute mastitis, diarrhea, disturbance of respiration, rectal prolapse and hair loss. Level of exposure to aflation also affect in ratio of milk yield. Milk production dropped within one week after exposure to 4 ppm from aflatoxin. In contrast lower level (0.4 ppm) can delay production drop for 3 to 4 weeks (Hutjens 1983).

Another character of aflatoxin exposure in dairy cattle is the conversion to AFM1 in milk (PRICE et al., 1985). Experiments have shown that milk will be free of aflatoxin after 96 hours of feeding non-contaminated feed. The level of aflatoxin in the feed and milk at the starting point will influence clearance time(Hutjens 1983; Lynch 1972).The concentration of AFM1 in milk seems to depend more on intake of AFB1 than on milk yield (Van der Linde et al., 1965). However, rapid increase of toxins in milk occur when milk yield is reduced as a result of high toxin intake (Masri et al. 1969). Toxin level in milk is also influenced by the rate of metabolism by the liver and rate of excretion by other routes (urine and feces) (Applebaum et al., 1982). High aflatoxin level in milk leads to the need for adding additives has the ability to reduce the aflatoxin level in milk. (Zakaria et al., 2019) reported that probiotics have significant effect on the reduction of AFM1 level in milk.

The results also indicate that there was no significant relationship between aflatoxin levels of diet and milk with milk yield, somatic cell count (SCC), milk protein and fat in the studied buffaloes. Researches indicated that different parameter of milk such as fat, protein, lactose and SNF milk is not influenced by dietary aflatoxin but it is noticed that these cows had low daily milk yield (Diaz-Nazario 2002). Dietary aflatoxin could have effect on protozoa population, rumen flora, and cause decrease in cellulose utilization, volatile fatty acid and ammonium production. Also, it cause increase in inactivity of alkaline phosphates enzyme in the rumen. These factors influences feed consumption, milk yield and composition(Diaz et al., 2004; Lanyasunya et al., 2005).

CONCLUSION

This study concludes that aflatoxins increase the risk of adverse birth outcomes (abortion, fetal resorption, stillbirth and retained placenta), in addition to there was no relationship between aflatoxin levels of feed and/or milk with milk production, somatic cell count, milk protein and fat

Aflatoxins are highly toxic to livestock and people. Even fed at non-lethal levels, aflatoxins can seriously impair animal health and productivity. Therefore, for pregnant and lactating cows and buffaloes, feeding ration should not contain aflatoxins and if present should not exceed 20 ppb to avoid exceeding the Food and Drug Administration level of 0.5 ppb in milk.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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Statement of animal rights:

All Institutional and National Guidelines for the care and use of animals were followed according to the Egyptian Medical Research Ethics Committee (no. 14 – 126)

AUTHOR CONTRIBUTIONS

Dr. Yahia and Dr. Asem have made substantial contributions to the research design, or the acquisition, analysis or interpretation of data; and to drafting the manuscript while the other authors revised it. All authors have approved the submitted version.

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