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Application of non-steroidal anti-inflammatory drugs (NSAIDs) for improvement of cattle fertility

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Abstract
Reproduction in the animals is the most important factor that not only affect the dairy farm profitability and the development of national economy but also it improves the living standard of rural and urban societies. Repeat breeding is a considerable problem in cattle breeding which leads to large economic losses due to increasing in the number of inseminations, increasing in the length of calving interval and moreover increasing in culling rates. A repeat breeder is generally defined as any cow that has not conceived after three or more services associated with true estrus. Gynaecological maneuvers induce inflammation and stress in animal which causes the releases of prostaglandins. Prostaglandins (PGF2α) is responsible for luteolysis, which may lead to decrease in progesterone level and the pregnancy is in compromised state. NSAIDs inhibit cyclooxygenase (COX) and thereby inhibits the synthesis of prostaglandins. This is how NSAIDs can be used for pregnancy maintenance.

Keywords: Repeat breeding, Fertility, NSAIDs, Meloxicam, COX

Introduction
Reproduction in the animals is the most important factor that not only affect the dairy farm profitability and the development of national economy but also it improves the living standard of rural and urban societies. Animal reproduction it directly or indirectly related to the economic parameters *viz*. milk production, reproductive culling, breeding cost and income through selling the calves. For flawless milk yield and optimal economic output, the cattle should give a calve at 12 months interval [1]. To accomplish this, there should not be a problem in a herd from the aspect of reproduction. There are numerous reproductive abnormalities which affect reproductive performance of animals.

Repeat breeding (RB) is a considerable problem in cattle breeding which leads to large economic losses due to increasing in the number of inseminations, increasing in the length of calving interval and moreover increasing in culling rates. A repeat breeder is generally defined as any cow that has not conceived after three or more services associated with true estrus [2].

The bovine conceptus produces interferon-tau (IFNτ) which prevents luteolysis over and above functional corpus luteum (CL) produces progesterone which is very much essential for supporting pregnancy [3]. There are two crucial periods of bovine pregnancy. The first period is first week after breeding and second period is from day 8 to 28, at which maternal recognition of pregnancy (MRP) takes place. Approximately 32% of total embryonic loss reported in this second period [4]. This leads the problem of repeat breeding.

There are several methods to regulate pregnancy *e.g.*

1. Use of progestogens (P_4) and prostaglandin F2 alpha (PGF2α) have been used to prevent the disorders related to estrus. But observation of estrus is necessary in administrations of P_4 and PGF2α.
2. GnRH and hCG application prior to the artificial insemination, together with the insemination or 1^{st} &15^{th} days after insemination because hormonal balance is very crucial in early embryonic period. Nearly, 25% of cattle embryos die within the first three weeks of pregnancy [5].
3. The latest method to regulate maternal and fetal relation, to retard or inhibit luteolysis, to maintain high progesterone levels and as a result; to enhance pregnancy rate is application of Nonsteroid Anti-inflammatory Drugs (NSAIDs) in critical days of pregnancy [6] In this method, NSAID drug inhibit the synthesis of cyclooxygenase (COX) enzyme and thereby it inhibits the production prostaglandin, so it is protecting CL.

Prostaglandins

Prostaglandins are lipid autacoids derived from essential fatty acid arachidonic acid. They maintain both homeostatic and pathogenic mechanisms. Prostaglandins and thromboxane A_2 (TXA_2), collectively termed prostanoids, are formed when arachidonic acid (AA), a 20-carbon unsaturated fatty acid, is released from the plasma membrane by phospholipases (PLAs) and metabolized by the sequential actions of prostaglandin G/H synthase, or cyclooxygenase (COX), and respective synthases [7].

NSAIDs

Nonsteroidal anti- inflammatory drugs (NSAIDs) are administered preliminarily for the pain management. NSAIDs produce analgesia primarily by inhibiting COX, thereby decreasing the production of prostaglandins that signal inflammation and pain as well as mediate physiologic functions such as platelet aggregation, gastric protection, and electrolyte balance in the kidney. The presence of at least 2 COX isoforms may account for variability in NSAID efficacy and toxicity both within and among species [8].

Table 1: Mode of action of NSAIDs

Class	Active ingredient	Effect
Cox-1 Specific Agents	Low Dose Aspirin	It makes COX-1 inhibition without doing COX-2 inhibition.
COX Non-specific Agents	Diclofenac, Ketorolak, Asetaminofen, Flunixin meglumine.	It inhibits both enzymes.
COX-2 Selective Agents	Meloxicam, Nabumetane, Nimesulid, Carpofren.	With Clinic threpautic doses in human and animals, while doing COX-2 inhibition, in increasing doses they cause COX-1 inhibition.
COX-2 Specific Agents	Celecoxib, Rofecoxib.	They are agents which do not cause COX-1 inhibition even in maximum threpautic clinical doses

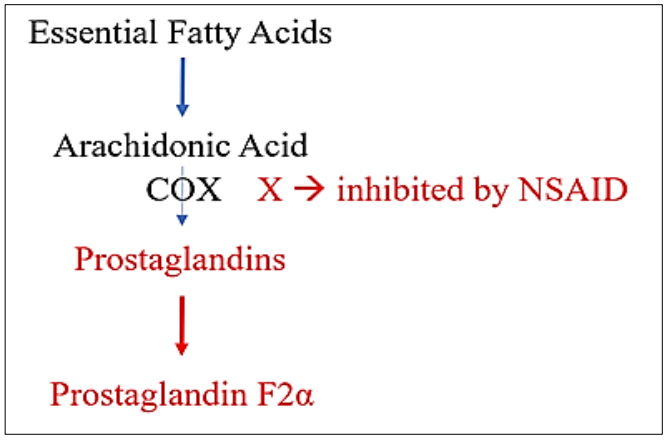

Fig 1: Mode of action of NSAIDs

Flunixin Meglumine (FM)

Flunixin meglumine is a derivation of nicotinic acid and is also a non-selective cox inhibitor. It is a potent NSAID and used for the treatment of the inflammation, pain and fever under control. Especially, it is used to control visceral pains. In addition to its analgesic effect, it has antiendotoxic and antipyretic effects. Flunixin meglumine's half-life is between 8 and 12 hours in cows, but it is longer in other animals [9].

Flunixin meglumine is used in cows in ways like intramuscular, intravenous and per os. When it is used orally, the dose is 1 mg/kg. 1.1-2.2 mg/kg dose is used in intravenous way. The most application way is intramuscular injection and the dose is 1.1 mg/kg. This dose of flunixin meglumine is given once in a day or two times by dividing the dose. Flunixin meglumine can be given in 6-8 hour intervals in 0.25-0.50 mg/kg doses. Average therapy period is three days and it can be given 5 days maximum [10].

Studies

Purcell *et al*. (2005) [11] studied effects of FM administration on ET of Angus-cross beef cows (n=748). The experiment involved the transfer of fresh or frozen bovine embryos to FM treatment at the time of ET improved pregnancy rates).

Merrill *et al*. (2007) [12] studied Effects of flunixin meglumine and transportation on establishment of pregnancy in beef cows (n=483). The result revealed that transportation of cows approximately 14 d after AI increased serum cortisol concentrations but did not affect AI pregnancy rates. However, treatment of cows with FM increased AI pregnancy rates, irrespective of whether they were transported.

Geary *et al*. (2010) [13] studied the effects of FM administration (n=1221) concluded that FM administration at 1.1 mg/kg of BW approximately 13 d after AI did not improve pregnancy establishment in beef cows and heifers and that the effects of handling heifers at this time may decrease pregnancy establishment.

Kasimanickam *et al*. (2018) [14] studied the effects of FM administration on Angus-cross beef cows (n = 710). There was improved pregnancy rates in excitable recipient cows following embryo transfer. The pregnancy rate for excitable recipient cows that did not received flunixin meglumine was lower compared to excitable recipient cows that received flunixin meglumine and calm recipient cows that did and did not receive flunixin meglumine. Excitable cows that did not receive flunixin meglumine had lower circulating progesterone concentrations, and greater cortisol, substance-P, PGFM and isoprostane 8-epi PGF2a concentrations.

Kasimanickam *et al*. (2019) [15] studied the effects of FM administration on Angus-cross beef cows (n = 1284). The results revealed improved plasma P_4 level in cows and improved pregnancy rates. The untreated cows shown higher amount of the cortisol, substance-P, PGFM and isoprostane 8-epi PGF2α compared with FM treated cows.

Carprofen

Carprofen is a propionic acid derivative NSAID and a selective cox-2 inhibitor. The drugs in this group take –fen suffix (*e.g.* ibuprofen, ketoprofen). Carprofen is the safest drug in this group because its peripheral prostaglandin inhibition is weak. It is a long effective NSAID with a clinical effect time of 12 hours. Carprofen in cows administered subcutaneous, in dose of 1.4 mg/kg to body weight [10].

Studies

Von Krueger & Heuwieser, (2010) [16] studied effect of flunixin meglumine and carprofen on pregnancy rates in of 413 Holstein-Friesian heifers. The result provided strong evidence that NSAID administered after AI do not improve

conception rates. This was true for 2 applications of FM (2.2 mg/kg of BW) on day 14/15 and 15/16 in dairy heifers and for 1 application of carprofen (1.4 mg s.c./kg of BW) in lactating dairy cows. Therefore, we discourage attempts to improve reproductive performance in dairy cattle by use of FM or carprofen in the dosage and administration schedule tested [16].
Heuwieser *et al*. (2011) [17] studied efficacy of carprofen on conception rates in lactating dairy cows after subcutaneous or intrauterine administration at the time of breeding on total 970 cattle. Their result revealed that subcutaneous treatment with the carprofen at the time of AI did not influence conception rate, whereas an intrauterine administration of carprofen 12 to 24 h after first AI had a negative effect on first-service conception rate in lactating dairy cows.
Torres *et al*. (2013) [18] carried out evaluation of treatments with hCG and carprofen at embryo transfer in a demi-embryo and recipient virgin heifer model (n=163). Their results revealed treatment with hCG plus carprofen at ET induced formation of secondary CL in 90% of heifers but decreased the luteotrophic effect of hCG, resulting in no effect on embryo survival.

Meloxicam
Meloxicam is a selective COX-2 inhibitor. It is an oxicam group NSAID. It has anti-inflammatory, analgesic and antipyretic effects. Half-life is 13 hours in cows. It is used in cows by intra-muscular, intra-venous and subcutaneous ways in single doses of 0.5 mg/kg [10].

Studies
Amiridis *et al*. (2009) [19] evaluated effect of combined administration of gonadotropin-releasing hormone, progesterone, and meloxicam for the treatment of the repeat-breeder cow (n=420). They made 4 treatment groups *viz*. GnRH, P_4, meloxicam, GnRH + P_4 + meloxicam. They found significantly higher pregnancy rates in the GnRH + P_4 + meloxicam group.
Erdem & Guzeloglu (2010) [20] studied effect of meloxicam treatment during early pregnancy in Holstein heifers (n=85). Their result indicated that administration of meloxicam at the time associated with pregnancy recognition processes to maintain the CL was harmful to the pregnancy even though the drug is safe during pregnancy in cattle.
Aguiar *et al*., (2013) [21] studied effect of meloxicam on pregnancy rate of recipient heifers following transfer of *in vitro* produced embryos. They experimented on total 207 cattle among total 105 cattle were given meloxicam treatment. They revealed that meloxicam had a positive influence on general pregnancy rate of treated heifers in comparison to non- treated heifers.
McDougall *et al*., (2016) [22] observed that addition of meloxicam to the treatment of clinical mastitis improves subsequent reproductive performance (n=509). They observed that use of the NSAID meloxicam, in addition to antimicrobial therapy for treatment of mild to moderate cases of clinical mastitis, results in a higher probability of bacteriological cure, and improved fertility in terms of higher conception to first service, higher probability of pregnancy by 120 d post-calving, a reduced number of inseminations required to achieve pregnancy and a tendency to have a shorter calving to conception interval.
Similarely, van Soest *et al*., (2018) [23] witnessed that addition of meloxicam to the treatment of bovine clinical mastitis results in a net economic benefit to the dairy farmer. The studey suggested that improvements in conception rate achieved by use of meloxicam, as additional therapy of mild to moderate CM in the first 120 d in milk, also have positive economic benefits. This inference remained true over a wide range of technical and economic inputs, demonstrating that use of meloxicam is likely to be cost effective across many production systems.

Tolfenamic acid
Tolfenamic acid (TA) is a non-steroidal anti-inflammatory drug and belongs to the group of fenamates. For inflammation associated with respiratory disease, the recommended dosage is 2 mg/kg by intramuscular injection into the neck area. Treatment may be repeated once after 48 hours [10].

Studies
Giammarco *et al*. (2018) [24] studied effects of a single injection of Flunixin meglumine or Carprofen postpartum on haematological parameters, productive performance, and fertility of dairy cattle. They observed highly significant improvement in pregnancy (35% vs 10%) at the first insemination in non-steroidal anti-inflammatory drug groups than in control was found. The findings evidenced that a single injection of FM or CA to non-febrile cows immediately after parturition could positively affect the metabolic adaptation of the cows at the onset of lactation and this aspect can positively influence reproductive performances and the culling rate.
Singh *et al*., (2020) [25] evaluation of the effect of GnRH analogue, progesterone and tolfenamic acid on serum progesterone profile and conception rate in repeat breeding crossbred cattle studied the effect of treatment by GnRH analogue - Buserelin acetate, Progesterone (P4) and Tolfenamic acid on 32 repeat-breeding crossbred cattle aged 3-8 years. All the animals were randomly divided into 4 equal groups (n=8). The result revealed that combination of Buserelin acetate, Exogenous P_4 and Tolfenamic acid therapy helps to maintain the P4 level and significantly increases the conception rate by 6 times than control group.

Conclusion
Gynaecological manoeuvres includes per rectal examination, artificial insemination, embryo transfer etc. are stressful conditions to the cattle, which may lead to the secretion of PGF2α. PG has negative effect on maintenance of pregnancy. Furthermore, repeat breeding syndrome is also very commonly encountered in the field. In both the conditions it is advised to administer any of the NSAID and if needed exogenous P4 and GnRH analogue. This will help in the improvement of the pregnancy.

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