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Review
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A HOLISTIC APPROACH TO THE EFFECTS OF INTRAUTERINE ANTIMICROBIAL THERAPY ON PREGNANCY RATE AFTER ARTIFICIAL INSEMINATION IN DAIRY COWS

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Abstract: Post-partum (pp) infertility following the artificial insemination (AI) can be a very common (around 50%) phenomenon in high-yielding dairy cows kept under poor management and feeding practices in particular. Even in clinically healthy females, intrauterine antimicrobial therapy (Lugol, Gentamicin, Rifaximin, etc.) may increase the fertility rate especially in those cows with latent (sub-clinical) intrauterine infection. Undoubtedly, modern animal husbandry requires to reduce possible calving losses with microbial origin that can prevent conception to occur and/or even terminate the ongoing pregnancy. In livestock farming/breeding, numerous obstacles (related to either the animal, humans or else) would prevent to achieve ultimate goals (regular reproductive cycle, insemination, pregnancy, calving, milking and dry period) that allow acceptable or minimum level of income (profit). For a sustainable herd health in profitable sectoral activity, individual females have to be in good health that would be achieved by strict rules to provide optimum animal productivity at animal welfare level. In this sense, a heavy physiological load of candidate mothers and their sustainable reproduction and milking requires at first good management and feeding practices. Beyond that, regarding the routine health services including treatment of dairy cows as appropriate, a 'holistic approach' is needed for an efficient therapy and speedy pp recovery of milking females. Otherwise, during the critical period, non-pregnant cows in open period may not conceive or peculiar delays in conception may become inevitable. Undoubtedly, in modern practice, holistic approach in farming/breeding animals requires effective management and feeding along with provision of appropriate health services towards meeting animal welfare level (sustainable high milk yield and regular calving annually). These ultimate aims would be easily facilitated by optimum management and good quality feeding, choosing the right individuals (age and breed) and working with dedicated care-takers and experienced Veterinarians. For the latter, provision of health services should incorporate comprehensive factors covering reproductive hormones, major vitamins-minerals and efficient antimicrobials (systemic and/or local) as needed. Finally, numerous profit-limiting factors (climate changes, heat-stress, water and food scarcity, market prices and residual problems) should also be dealt with a great care. Otherwise, undesirable outcomes (ovarian, uterine and mammary disorders) in dairy farming would be inevitable as commonly seen worldwide.

Keywords: Breeding, Cattle, Fertility, Infection, Treatment, Uterus

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1. Introduction

Reproductive problems (Arthur et al., 1993; Ptaszynska, 2001; Sönmez, 2012; Tohumcu, 2015) are common especially in cross-bred (Brown Swiss and Simmental) cows (Figures 1a and 1b) rather than low-yielding local (indigenous) breeds (Figure 1c) in the Eastern/South-Eastern Anatolia regions (Uçar, 2006; Uçar et al., 2020). Most metabolic disorders (Aktaş et al., 2011; Uçar et al., 2011; Ömür et al., 2016) coincide with indoor shelters during winter (Uçar, 2006; Uçar et al., 2009) that lead the population to unfavourable conditions (warm, crowded or dark environment) along with inadequate management and feeding (Uçar et al., 2004, Uçar, 2006; Çolak and Uçar, 2007; Uçar et al., 2011; Uçar et al., 2020). In Western Anatolia, where industry-dominated dairy breeds (mainly Holstein) are preferred, such problems are frequently encountered in high-yielding dairy cows (Uçar et al., 2020) under inadequate hygiene and/or welfare problems (Dwyer, 2020). Non-pregnant dairy cows cost a loss of approximately 7 US dollars/day per milking animal. In these peculiar infertility cases (Daşkın, 2005b; Gökçen, 2008), considering the length of days spent in a dairy herd, the amount of milk loss per day, the higher number of non-pregnant animals, and the excessive costs of management-feeding, health and labour as well as the unaffordable rate of economic loss will be even much higher (Daşkın, 2005a, b; Öztürkler and Uçar, 2006; Uçar et al., 2011).

In this challenging period, in terms of metabolic health and reproductive efficiency, appropriate reproductive herd management (Daşkın, 2005b) starting before

calving and ideal care-feeding (Uçar et al., 2004, Uçar et al., 2011; Uçar et al., 2020) contribute to obtaining appropriate body condition score (BCS) at intermediate level (around 3.00 unit, 1-5 scale) (Daşkın, 2005b; Çolak and Uçar, 2007; Uçar et al., 2011). Likewise, sufficient energy (barley/maize, concentrated feed, silage, quality grass/clover) (Uçar et al., 2004; Uçar et al., 2011) and regular vitamin-mineral supplements (such as vitamins of A-D-E, and minerals/elements of calcium, phosphorus, sodium, potassium, chloride, iron, copper, zinc, selenium, etc.) in normally fed pregnant females positively affect metabolic and reproductive parameters (Kaçar et al., 2008; Uçar et al., 2011; Ömür et al., 2016) (Figures 2a, 2b). On the other hand, in the case of insufficient management-feeding (Polat et al., 2009; Uçar et al., 2011) in enterprises where traditional animal husbandry (Uçar, 2006; Tohumcu, 2015) instead of modern animal husbandry (Uçar et al., 2020) is applied, the reproduction processes may be disrupted (Uçar et al., 2011) or completely stopped (Uçar et al., 2004) (Figure 2c). Obviously, holistic (conditional, hormonal and antimicrobial) approaches are critically important for the solution of reproductive problems (Öztürkler and Uçar, 2003, 2006; Uçar, 2006; Gökçen, 2008; Dwyer, 2020; Uçar et al., 2020; Uçar, 2021).

2. Metabolic Changes during Peri-Parturient Period in Dairy Cows

By the end of advanced pregnancy (Arthur et al., 1993; Sönmez, 2012), cows enter the transition period (especially between pre-/post-partum 21 days) (Ömür et al., 2016), as partially overlapping with the dry period (involving 45-75-day pre-partum) (Arthur et al., 1993; Ptaszynska, 2001; Weber et al., 2021). The periodic time flow during these critical processes are roughly as follows; a) colostrum release at calving (Figure 3) and the onset of early lactation period (up to 55th day pp) (Aktaş et al., 2011) (Figures 1c, 2b), b) the immediate shedding of foetal membranes (Figure 1a) in the uterus followed by prolonged involution (up to day 42 pp) (Arthur et al., 1993), c) gradual intrauterine bacterial elimination (up to day 53 pp) (Daşkın, 2005b), d) as coinciding with the end of early lactation period (Aktaş et al., 2011), e) the progesterone hormone returns to normal cycle levels (if there is no new pregnancy until the days 56-63rd) (Daşkın, 2005b), f) settling the ovarian luteal/follicular cycle and uterine glands returning to their normal (excretory) function (if there is no infection) (Arthur et al., 1993; Gökçen, 2008; Sönmez, 2012), g) removal of ketone bodies from the blood (Uçar et al., 2004; Aktaş et al., 2011; Ömür et al., 2016) and finally h) occurrence of new pregnancy following oestrus (and artificial insemination) (Sönmez, 2012) only after the first oestrus cycle of 13-26 days long, as the earliest time (Ptaszynska, 2001; Daşkın, 2005b; Gökçen, 2008).

However, the early lactation period (Aktaş et al., 2011) overlaps with the involution and bacterial elimination of the uterus (Daşkın, 2005b) and mobilisation of fat depots of the body due to NEB (negative energy balance) (Uçar et al., 2004; Gökçen, 2008; Aktaş et al., 2011) mainly because of the heavy physiological load of ongoing lactation (Aktaş et al., 2011). Collectively, these extremely critical physiological events would presumably worsen the reproductive health at any time (Uçar et al., 2004; Gökçen, 2008; Uçar et al., 2011). In this period, intrauterine bacterial elimination (from 100% at calving to 10% until day 53rd pp) occurs normally during the uterine involution as coinciding with the continuous improvement in BCS, *i.e.* body fat deposits (mainly located at subcutaneous region) (Uçar et al., 2004; Daşkın, 2005b; Çolak and Uçar, 2007; Gökçen, 2008). Due to high lactation and malnutrition (Uçar et al., 2004), progesterone deficiency (Daşkın, 2005a, b) may occur as a result of *lipolysis*, then ketone bodies are removed from the systemic blood as a result of ketosis (*gluconeogenesis*), which can last up to the 83rd day (Uçar et al., 2004; Daşkın, 2005b; Aktaş et al., 2011).

(a) (b) (c)

Figure 1. a) Retentio secundinarum, b) calving by Caesarean operation in a heifer, and c) suckling (bad-tempered) cow with normal calving.

Figure 2. a) Artificial insemination-bearing bull-calf (8 months-old), b) 10 days-old artificial insemination calf suckling, and c) orally inserted magnet firmly attached with an old sharp metal piece (permanently perforating the reticular wall leading to chronic severe pericarditis) as resulted in sudden death of cow (with 4.5-months pregnancy) under treatment.

Figure 3. Colostrum feeding of Simmental artificial insemination calf born after dystocia.

Under the normal conditions, cows should become pregnant again by day 85 pp (Uçar et al., 2011). Otherwise, candidate mothers that cannot conceive following the artificial insemination due to various reproductive problems may become "*infertile*" after 90 days (Öztürkler and Uçar, 2006; Gökçen, 2008) and especially after 120 days, they are called as "*repeat breeder*" (İleri et al., 2002) (Figures 4a, 4b, 4c).

3. Clinical Approaches for Treatment of Genital Disorders in Post-Partum Dairy Cows

Major reproductive hormonal (Öztürkler et al., 2001a; Uçar et al., 2009; Polat et al., 2009) and inflammatory disorders (Öztürkler et al., 2001a, Öztürkler et al., 2001b; Öztürkler and Uçar, 2006; Weber et al., 2021) are frequently observed in high-yielding (Daşkın 2005b; Gökçen, 2008; Uçar et al., 2020), poorly managed-fed pp cows (Uçar et al., 2004; Uçar, 2006; Uçar et al., 2011; Uçar et al., 2020).

When the applications that increase the success of artificial insemination in animals receiving medical (Veterinary) services over the years are evaluated (Öztürkler and Uçar, 2003; Uçar, 2006, 2021), it is seen that cows frequently encounter clinical findings (anoestrus, *retentio secundinarum*) (Figure 1a) or latent reproductive problems (*suboestrus*, *subclinical endometritis*) originating from both the ovary (mainly hormonal) (Öztürkler et al., 2001a; Polat et al., 2009) and the uterus (inflammatory and/or hormonal origin) (Öztürkler et al., 2001a; Öztürkler and Uçar, 2003, 2006). In this context, in one hand, relevant hormones (mainly $PGF_2\alpha$, GnRH, hCG, progesterone) are used alone (Polat et al., 2009) or together as a combined protocol (Daşkın 2005b; Uçar, 2006; Uçar et al., 2009; Uçar et al., 2011) for either synchronisation and/or therapeutic (anoestrus, delayed puberty) purposes (Arthur et al., 1993; Ptaszynska, 2001; İleri et al., 2002). On the other hand, antimicrobial approaches are also important in sub-clinical or clinical cases of inflammatory origin (Öztürkler and Uçar, 2003; Uçar, 2021). Both systemic (injectable penicillin, cephalosporin, etc.) (Ptaszynska, 2001; İleri et al., 2002) and intrauterine antimicrobial (local) treatment solutions (Öztürkler et al., 2001a; Öztürkler et al., 2001b) can be used against possible (*subclinical endometritis*) (Öztürkler et al., 2001b) or clinical uterine disorders (*endometritis*) leading to infertility/repeat breeding (Ptaszynska, 2001; İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008). Undoubtedly, local treatment approaches (Öztürkler et al., 2001b; Uçar, 2021) for combatting/eliminating the source of actual microbial problem (Daşkin, 2005a, b; Gökçen, 2008) are critical in the field (Öztürkler and Uçar, 2003, 2006; Uçar 2006). In this context, different antimicrobial agents, such as simple Lugol solution (2% iodine) (İleri et al., 2002) as an antiseptic or Rifaximin spray, Oxytetracycline, Gentamicin sulphate (300-400 mg) (Öztürkler et al., 2001a; Öztürkler et al., 2001b; Öztürkler and Uçar, 2003, 2006) or Cephalosporin (Ptaszynska, 2001) as antibiotics are frequently used in the field.

(a)

(b)

(c)

Figure 4. a, b) Simental artificial insemination calves of a repeat breeder Simmental mothers treated, and c) Cross-bred (Simmental x Holstein) artificial insemination calf of a repeat breeder Holstein mother treated.

However, in our world under the threat of global warming and climate change (Gardner, 2015), issues such as green energy, ecological agriculture, organic livestock breeding and animal welfare (Dwyer, 2020) are gaining more priority in the modern world (Gökçen, 2008; Uçar et al., 2020; Uçar, 2021). In modern animal breeding culture (Uçar et al., 2020) therefore, residual concerns (for milk and meat) (BAYNOVA Catalogue 2021) encountered when using preventive/therapeutic agents/drugs and organic livestock farming (Gardner, 2015) has become more popular especially in "Disease Free" (especially for Brucellosis and Tuberculosis) dairy cattle farms (İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008, Sönmez, 2012).

In western parts of our country (especially Marmara, Aegean and Mediterranean regions), reproductive disorders are very common especially in high-yielding dairy farms of certain (large) sizes (Daşkın, 2005b; Gökçen, 2008; Uçar et al., 2020, Uçar, 2021). Of course, the expected infertility (mainly subclinical endometritis) cases, as commonly seen in the field (Gökçen, 2008; Sönmez, 2012), can be prevented by intrauterine treatment (Öztürkler and Uçar, 2006) and thus the economic (milk/meat) losses of the enterprises (Daşkın, 2005b) and the risk of residues (BAYNOVA Catalogue, 2021) are reduced in high-yielding dairy cows. Intensive breeding culture may bring high heat stress, high contamination (respiratory, digestive, feet, udder, uterus) problems (BAYNOVA Catalogue, 2021) in crowded herd especially kept in semi-closed areas (Uçar, 2006; Gökçen, 2008; Gardner, 2015; Weber et al., 2021). Indeed, about half of the oestrus signs observed in cows go unnoticed in dairy farms (İleri et al., 2002; Gökçen, 2008). Moreover, in the field, a worldwide average of 50% conception is observed in the first artificial insemination of cows (Arthur et al., 1993; Öztürkler and Uçar, 2003; Gökçen, 2008; Uçar, 2021). In this case, the loss/missed chance of conception can reach up to 75% following the insemination under poor farming/breeding practices in particular (Gökçen, 2008; Kaçar et al., 2008; Uçar et al., 2011). In addition to the classical intrauterine treatment (by using Gentamycin, Cephalosporin, Rifaximin) commonly used in the field (Ptaszynska, 2001; Öztürkler et al., 2001a; Öztürkler et al., 2001b; Öztürkler and Uçar, 2006), new potential disinfectant/antioxidant as effective agents in respiratory (Bursalı et al., 2021) and digestive systems (Apaydın Yıldırım, 2021) such as Active Anionic Oxygen (AAO) (BAYNOVA Catalogue, 2021) have recently been postulated to contribute positively to fertility in dairy cows (as also proven by our preliminary results, unpublished data). Undoubtedly, the strategic importance of national production of such "organic" solutions in addition to commercial non-organic products (such as Gentamycin, Cephalosporin, etc.) effectively used in health problems (foot, udder, uterus, lung and digestive system) encountered in dairy enterprises (Daşkın, 2005b; Gökçen, 2008) would be of great importance (Uçar, 2006; Apaydın Yıldırım, 2021; Uçar, 2021). This situation may be extremely important both for the legislators of the breeding sector (fulfilling the expectations of the European Union from our country as EU candidate) (Daşkın, 2005b¸ Gökçen, 2008; Uçar, 2021) and for the consumers (BAYNOVA Catalogue, 2021).

4. Discussion

Considering the farmers/breeders, veterinarians and other sector stakeholders experiencing economic difficulties, the need for healthier and highly productive animals is obvious (Uçar, 2021). Surely, achieving high individual productivity (milk, meat and calves) in dairy herds is possible only with the sustainable health for animal welfare as part of effective herd management (Daşkın, 2005b; Gökçen, 2008). Strategic approaches for one world and one health towards ecological farming/breeding are essential in modern animal

husbandry (Uçar et al., 2020; Dwyer, 2020). By doing so, clean (green) products provide environmental awareness that would help meeting sectoral higher standards in food chain (BAYNOVA Catalogue, 2021).

Therefore, it is vitally important both to spread the awareness culture in breeding animals and to increase the sectoral solidarity among stakeholders in terms of ideal solution to the genital problems encountered in dairy farms (Daşkın, 2005b; Gökçen, 2008; Uçar, 2021). Of course, genitally healthy cows conceive faster, give healthy calves more often and have higher milk yield. These healthy animals (presumably free from uterine infections) can also remain healthy and productive longer on the farm. The ultimate goal for a given herd should therefore be preventing common infertility cases with microbial origin (İleri et al., 2002; Daşkın, 2005b; Gökçen, 2008) through locally effective (Öztürkler and Uçar, 2003; Uçar, 2006) and/or preferably organic treatment (BAYNOVA Catalogue, 2021) in high-yielding dairy cows. Thereby, reducing economic losses (Daşkın, 2005a, b; Gökçen, 2008) and minimising possible residual risk (in milk/meat) (BAYNOVA Catalogue, 2021) in dairy farm would be possible to reach a modern livestock breeding standards (Uçar et al., 2020; Dwyer, 2020; Uçar, 2021).

At last, regarding profitable livestock farming and breeding (Daşkın, 2005b), other critical factors such as recent climate changes, excessive heat-stress during indoor sheltering, environmental water and food scarcity (Uçar, 2006; Uçar et al., 2011; Gardner, 2015), and high market prices should also be dealt with an utmost care. Moreover, subclinical metabolic disorders (Uçar et al., 2004; Aktaş et al., 2011) lowering calf (Gökçen, 2008) and milk yields (Weber et al., 2021) have to be monitored carefully. By doing so, high standards of management and feeding (Uçar et al., 2020) and animal welfare levels (Dwyer, 2020) would be more achievable as part of modern practices in livestock farming/breeding (Daşkın 2005a, b; Gökçen, 2008; Uçar, 2021).

5. Conclusion

Collectively, ideal and profitable herd management in dairy farms should incorporate efficient reproductive management of females (and breeding males), candidate/pregnant mothers and milking cows. For these aims, comprehensive factors covering; i) regulatory hormones (GnRH, Progesterone, hCG, PMSG, $PGF_2\alpha$) (Öztürkler et al., 2001a; Öztürkler and Uçar, 2006; Polat et al., 2009; Uçar et al., 2009), ii) major vitamins (A, D, E) (Kaçar et al., 2008; Uçar et al., 2011; Ömür et al., 2016) and iii) minerals (calcium, phosphor, sodium, selenium, potassium, chloride, zinc, copper, manganese, etc.) (Uçar et al., 2011; Ömür et al., 2016) should be provided appropriately (Figure 5a). Also, systemic (Penicillin; Penicillin plus Clavulonic acid, Cephalosporin, Oxytetracycline, etc.) and/or intrauterine antimicrobials (Lugol, Gentamicin, Rifaximin, Cephalosporin, etc.) can be used as needed for reproductive inflammations effectively (Ptaszynska, 2001; Öztürkler et al., 2001b; İleri et al., 2002; Öztürkler and Uçar, 2006; Uçar, 2006) (Figure 5b). Also, a recent disinfectant/antioxidant product (AAO) (BAYNOVA Catalogue, 2021) have also been proposed for residue-free and immediate therapy for numerous inflammations including pulmonary, mammary and possibly uterine disorders. For the latter (AAO) treatment, these recent findings should be confirmed widely in livestock breeding and farming.

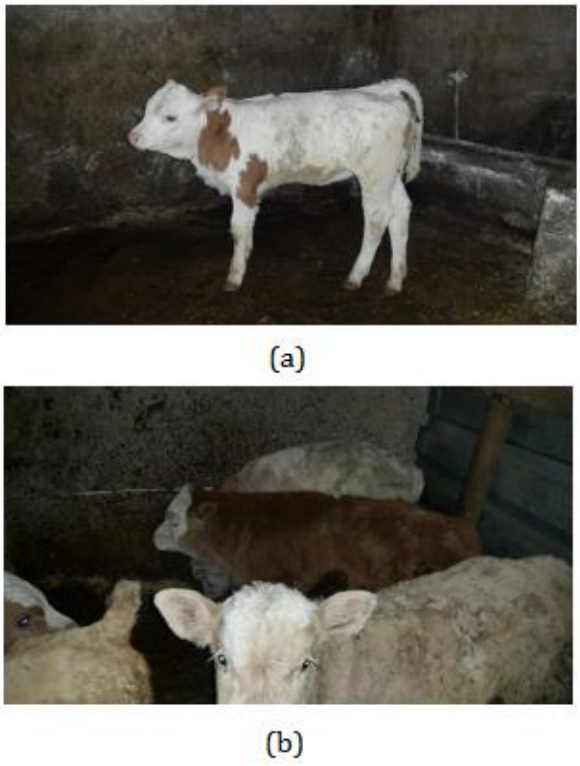

Figure 5. a) Simmental artificial insemination calf born from an infertile mother treated with hormones and vitamins, and b) cross-bred artificial insemination calves born mostly from infertile mothers treated with hormones and vitamins as needed.

Author Contributions

Concept: Ö.U. (50%) and D.A. (50%), Design: Ö.U. (50%) and D.A. (50%), Supervision: Ö.U. (50%) and D.A. (50%), Literature search: Ö.U. (50%) and D.A. (50%), Writing: Ö.U. (50%) and D.A. (50%), Critical review: Ö.U. (50%) and D.A. (50%), Submission and revision Ö.U. (50%) and D.A. (50%). All authors reviewed and approved final version of the manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

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