Ovsynch based protocols in reproductive management and infertility treatment in dairy cows - when and why?

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Abstract

In order to optimise reproductive performance and thus production, it is now impossible to control the reproduction of dairy cows without the use of hormones. Due to the characteristics of dairy cows, the use of hormones not only reduces the need for visual heat detection and thus the number of undetected cows in heat, but also prevents certain problems associated with intensive production and its negative effects on reproduction. Ovsynch, as a planned combination of GnRH and $PGF_{2\alpha}$ that allows artificial insemination at the optimal time without the need to control ovaries and uterus, once offered solutions to these problems, but over time its shortcomings were recognised. Therefore, pre-synchronisation protocols have been developed to create optimal conditions for Ovsynch and allow for the best outcome. In addition to pre-synchronisation, Ovsynch and its modifications can also be used in the resynchronisation of inseminated and sonographically diagnosed non-pregnant cows as soon as possible, improving farm efficiency. The addition of progesterone implants also further improves the performance of Ovsynch-based protocols. In addition to controlling reproduction, Ovsynch and its modifications have also proven successful in treating certain forms of infertility in dairy cows, such as anovulatory conditions and cystic ovarian disease. This paper presents the possibilities of using the Ovsynch protocol and its various modifications, and their advantages and disadvantages.

Key words: *dairy cow; Ovsynch; pre-synchronisation; resynchronisation; GnRH;* $PGF_{2\alpha}$

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Introduction

In modern dairy farming, satisfactory production cannot be achieved without optimal reproduction. In recent decades, several protocols have been routinely used in reproduction management on dairy farms (Pursley et al., 1997; Morini et al., 2019), with the aim of minimising and/or avoiding the most stressful events in production (oestrus detection, treatment of postpartum anoestrus, shortening the calving interval) (Lojkić et al., 2018; Dobos et al., 2022). Most of these protocols are based on the administration of hormones for oestrus induction and synchronisation of ovulation, allowing for fixed time artificial insemination (FTAI). The most commonly used hormones are synthetic analogues of gonadotropin releasing hormone (GnRH) in combination with natural or synthetic analogues of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). In short, GnRH has a role to stimulate follicular growth, development and ovulation, while $PGF_{2\alpha}$, which has a luteolytic effect, enables the development of a new oestrous cycle. The aim of this paper is to give a brief overview of the protocols used from professional point of view.

Synchronisation of ovulation

The best-known protocol for oestrus synchronisation based on the administration of GnRH and $PGF_{2\alpha}$ is Ovsynch (Pursley et al., 1995). This protocol was developed with the goal of tight synchronisation of ovulation, by synchronising follicular development, in a way that allows for a single timed artificial insemination (TAI) with satisfactory conception rates (Laven, 2019). The protocol begins with the first GnRH administration randomly during the oestrous cycle, followed seven days later by $PGF_{2\alpha}$. The second GnRH is administered two days after $PGF_{2\alpha}$, allowing for FTAI 16 (8-24) hours after the last GnRH administration (Kasimanickam, 2015). The role of the first GnRH is to induce ovulation of the follicle present in the ovary at the time, leading to corpus luteum (CL) formation. Efficiency in inducing ovulation varies from 66–85%, and depends on the stage of follicular development at the time of administration. The role of the $PGF_{2\alpha}$ administered 7 days later is to cause luteolysis, thus enabling further development of a new follicular wave that started when ovulation of the present follicle was induced (Nowicki et al., 2017). The role of the second GnRH, administered on the 9th day is to synchronise the event of ovulation of the dominant follicle of this new follicular wave (Fricke, 2001) that started to develop after the first GnRH. Artificial insemination (AI) is performed 16-24 hours after the second GnRH (Nowicki et al., 2017). This protocol is most efficient in lactating cows, less efficient in anoestrus cows and least efficient in heifers (Laven, 2019). The greatest advantage of Ovsynch is the tight ovulation synchronisation, allowing for AI without prior oestrus detection (Kasimanickam, 2015). Oestrus detection is a growing problem in modern dairy farms, affecting 10-40% of farms. The reason may be poor oestrus expression, though the shortening of oestrus and weakening of signs of heat are common in high yielding dairy cows. This is likely due to the negative energy balance and correlated metabolic and endocrinologic disturbances (Brozos et al., 2021; Sangsritavong et al., 2002), including lower LH and oestrogen concentrations. Synchronization protocols like Ovsynch offer a solution for this kind of reproductive problem, by enabling AI without previous oestrus detection (Nowicki et al., 2017).

Furthermore, Ovsynch could provide a solution for farms affected with heat stress, as one of the causative factors for decreased reproductive efficiency (Nowicki et al., 2017). However, Ovsynch has some shortcomings, even in lactating cows, where up to 40% of animals do not respond to this protocol, either due to insufficient synchronisation of follicular waves, or failed luteolysis (Martins and Pursley, 2016). In the first case, in cows whose dominant follicles do not respond to the first GnRH, the reason is probably a follicular age of 3-4 days of at the time of the first GnRH, when there is a possibility of their submission to atresia before $PGF_{2\alpha}$ administration. In this situation, the new emerging follicular wave with new dominant follicle will not respond with ovulation at the second GnRH administration (Laven, 2019.). The solution is pre-synchronisation of cows, which should result with cows in days 5 to 9 of the cycle at the first GnRH administration (Vasconselos et al., 1999; Bello et al., 2006). The second problem encountered in Ovsynch is a failed response of CL to $PGF_{2\alpha}$ application. The lack of luteolytic effect results in suppressed growth of the second follicular wave, thus disabling synchronisation of ovulation and FTAI (Nowicki et al., 2017.). Percentage of cows in which luteolysis was not induced varied between 10–11%. This number can be lowered by the application of the second $PGF_{2\alpha}$ 24h after the first application (Laven, 2019).

The greatest results are obtained when Ovsynch is used at the herd level. This strategy allows synchronous insemination of a large number of postpartum cows and increases the pregnancy rate in the herd. When used on a single, problematic animal, increase in pregnancy rates cannot be expected (Nowicki et al., 2017). The second shortcoming of Ovsynch is decreased success in improving pregnancy rates in heifers, especially when compared to insemination at observed oestrus. For this reason, heifers are submitted to modified protocols (Laven, 2019) (Fig. 1). One Ovsynch modification is Cosynch, a protocol based on Ovsynch in which the animals are inseminated at the time the second GnRH is applied. In this way, the animals are handled one time less, which is very important from the management perspective (Rabiee et al., 2005); however, the results obtained in dairy cows are not optimal (Fricke, 2001). The Select Synch protocol is similar to Cosynch, but lacks the final GnRH administration awaiting the onset of oestrus (Rabiee et al., 2005). The overall success of Ovsynch and Select Synch is very similar, though Select Synch has the (dis)advantage of depending on oestrus detection for AI (Rabiee et al., 2005).

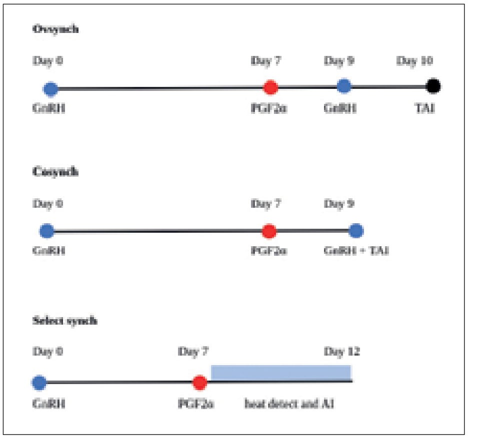

Figure 1. Ovsynch and its modifications
TAI- timed artificial insemination; AI- artificial insemination

Pre-synchronisation protocols (Fig. 2) have been developed as a modification of the original Ovsynch protocol, due to the fact that the protocol results are influenced by the phase of the oestrous cycle in which synchronisation starts (Fricke, 2001; Rabiee et al., 2005). Ovsynch programs that start too early, *i.e.*, 1-4 days after ovulation, or too late, *i.e.*, 13-

20 days after ovulation, result in fewer synchronised animals. Furthermore, depending on the domination phase of the preovulatory follicle (before or after domination phase) at the time of the first GnRH application, ovulation might not be achieved, and thus no synchronous new wave will be obtained. The best response is achieved when the first GnRH is applied between 5th and 9th day of cycle (Vasconcelos et al., 1999; Rabiee et al., 2005). Pre-synchronisation protocols have a role of ensuring this phase of cycle for the beginning of Ovsynch (Kasimanickam, 2015).

One of them, Presynch-Ovsynch, is based on administration of $PGF_{2\alpha}$ to synchronise the cycles for Ovsynch. Presynch begins with the administration of $PGF_{2\alpha}$ 12 days before the scheduled Ovsynch, synchronising ovarian activity and ensuring the presence of second wave follicles in the ovaries at the time of the first GnRH application (Moreira et al., 2001). Several authors suggest that the Presynch should consist of two $PGF_{2\alpha}$ administrations 14 days apart, with the second given 10-14 days before the planned Ovsynch (Moreira et al., 2001; El-Zarkouny et al., 2004; Navanukraw et al., 2004; Galvao et al., 2007). Dirandeh et al. (2015) recommend the onset of Ovsynch 7 days after the second $PGF_{2\alpha}$ at pre-synchronisation. The pregnancy rates achieved are 8% higher when pre-synchronisation is used (Gumen et al., 2012), while El-Zarkouny et al. (2004) found a pregnancy rate of 48.8% in pre-synchronised animals, compared to 37.5% in cows synchronised with Ovsynch only.

The G6G protocol begins with $PGF_{2\alpha}$ application, which serves to luteolise the functional CL. Two days later, GnRH is administered to induce ovulation (Bello, et al., 2006). Their joint task is to initiate a new oestrous cycle. Ovsynch is then started 6 days after GnRH, when cows should be in day 6 of the cycle. A dominant follicle able to ovulate after the first GnRH of Ovsynh is expected in the ovaries of cows synchronised in this way (Bello et al., 2006; Kasimanickam, 2015).

The Double Ovsynch is a modification of the basic Ovsynch, in which two Ovsynch protocols are applied 7 days apart (Souza et al., 2008). FTAI follows after the second Ovsynch. Compared to Presynch, Double Ovsynch results in higher pregnancy rates (49.7% and

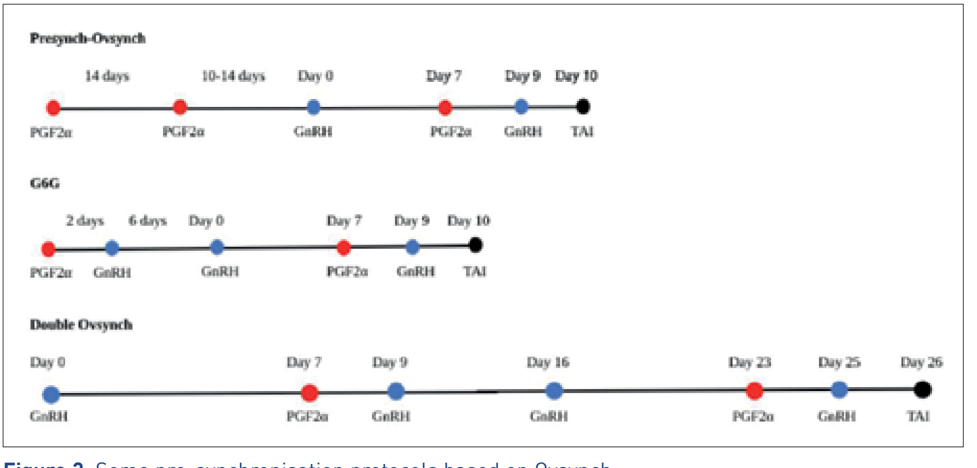

Figure 2. Some pre-synchronisation protocols based on Ovsynch
TAI- timed artificial insemination; AI- artificial insemination

41%, respectively). The explanation could be that cows with postpartum inactive ovaries do not respond to $PGF_{2\alpha}$ application in Presynch. On the other hand, two additional GnRH applications in Double Ovsynch stimulate the ovaries to return to cyclic activity. In cows with normally active ovaries, Double Ovsynch had no negative effect. Furthermore, Double Ovsynch achieved better results in heifers than cows (65.2% and 37.5%, respectively). Therefore, Double Ovsynch is recommended for use in heifers, while other $PGF_{2\alpha}$ pre-synchronisation protocols, such as Presynch, are recommended for cows (Nowicki et al., 2017).

Progesterone supplementation for a duration of 7 days, starting with the first GnRH and ending with $PGF_{2\alpha}$ application in Ovsynch, can be used for oestrus induction and synchronisation of ovulation in cows and heifers (Brozos et al., 2021). They are most commonly used in anoestrus cows and heifers, and in cows with cystic ovarian disease (COD) (Kasimanickam, 2015). Intravaginal application of controlled internal drug release (CIDR) or progesterone releasing intravaginal device (PRID) releases a certain amount of progesterone, which is sufficient for oestrus appearance in cows after removal of the device (Fricke, 2001). McDougall (2010) showed that the vast majority of cows showed no signs of oestrus at the beginning of spring breeding season, and 73% had no detectable CL at the start of the synchronisation programme. In addition, both Ovsynch and Ovsynch with progesterone supplementation were found to reduce the number of days open, while progesterone supplemented Ovsynch reduced the number of days open for 6 days more than with basic Ovsynch. Therefore, Ovsynch with progesterone supplementation is a good solution for herds where anoestrus cows are a significant problem (Laven, 2019).

Resynchronisation protocols can be used for cows that fail to conceive to TAI, (Parkinson, 2019) (Fig. 3). The key role in dairy farm management is to accurately identify these animals. Early pregnancy diagnostics should focus on detecting non-pregnant cows. Their subsequent submission to the next AI procedure increases reproductive efficiency and pregnancy rates, and shortens the period between two AIs (Fricke, 2001). Ovsynch can also be used for resynchronisation and allows AI 33-40 days after the previous AI, after the cow has been diagnosed as non-pregnant. This period can be further

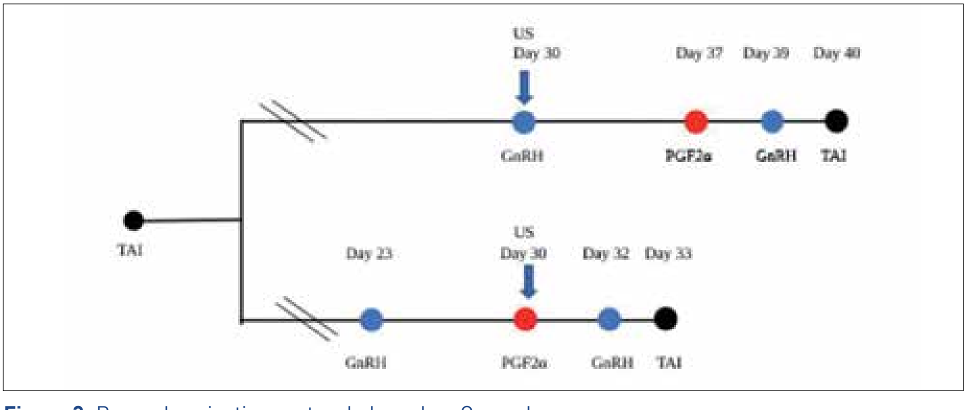

Figure 3. Resynchronisation protocols based on Ovsynch
US- ultrasound pregnancy detection; TAI- timed artificial insemination

shortened, by administering GnRH 7 days before the planned sonographic examination. In this way, $PGF_{2\alpha}$ can be administered on the day of pregnancy diagnosis in non-pregnant cows, and these cows can be inseminated in three days (Špoljarić et al., 2017). Pregnancy rates obtained when resynchronisation starts between 23 and 25 days after the previous AI vary between 23 and 50%, while pregnancy rates drop to 25.2 to 33.6% when it starts between 30 and 32 days post-AI (Nowicki et al., 2017). PRID and CIDR devices can also be used for oestrus synchronisation in cows that have failed to conceive after the first TAI. One protocols using progesterone is the Fastback programme, where progesterone devices are inserted 14 days after TAI, removed 7 days later (21 days after TAI), and cows are observed between 22 and 25 days after TAI for possible signs of oestrus. This increases the number of non-pregnant cows that are re-inseminated after failed conception at the first AI (Laven, 2019).

Use in heifers and cows

Compared to AI at observed oestrus, where the conception rates achieved are between 50-60%, Ovsynch in heifers results in lower conception rates, usually between 30–40% and FTAI is not so readily used. The reason for this is the different follicular dynamics between cows and heifers, for in the latter, oestrus is visible very soon after $PGF_{2\alpha}$ application, resulting in asynchronous ovulation for FTAI (Risco, 2015). Therefore, modified protocols are required (Laven, 2019). Double Ovsynch is one of the protocols that can be used to prevent asynchronous ovulation (Nowicki et al., 2017). Furthermore, PRID or CIDR devices in combination with Ovsynch modification result in an increased conception rate, compared to observed oestrus insemination after $PGF_{2\alpha}$ application (57% and 48%, respectively) (McDougall et al., 2013), but only when heifers were inseminated together with the second GnRH administration. Similar results are obtained with administration of Cosynch in heifers (Laven, 2019), although conception rates may be 3 to 4% lower, the advantage being one less animal handling (Colazo and Mapletoft, 2014). Conception rates in heifers using the Cosynch modification where the CIDR device is administered at the time of the first GnRH administration, and removed 5 days later with $PGF_{2\alpha}$ application, and the second GnRH is administered 72 h later at the same time as AI, vary between 50 and 60% (Risco, 2015). The combination of progesterone devices and $PGF_{2\alpha}$ is also used. In these protocols, the progesterone device is administered at the beginning of the protocol, $PGF_{2\alpha}$ is applied on day 6, and the progesterone device is removed one day later. Subsequent AI can be performed once at 56 hours, or twice at 48 and 72 hours after removal of the progesterone device (Laven, 2019). When comparing these two programmes (Cosynch and progesterone-$PGF_{2\alpha}$), no difference in pregnancy rates is observed (52.4 *vs.* 54.8%, respectively) (Sahu et al., 2015). The price of progesterone-$PGF_{2\alpha}$ is much lower compared to Cosynch, but Cosynch requires one less handling of the animal (3 and 4, respectively). These two variables must therefore be taken into account when selecting appropriate protocols for each individual farm (Colazo and Mapletoft, 2014; Laven, 2019).

Use in fertility problems

Anoestrus occurs physiologically in cows after parturition. This condition is considered a multi-causal pathology when ovarian cyclic activity does not return in the expected time when animals need to be bred again (Parkinson, 2019), when treatment is required. Hormonal treatment aims to cause a rebound effect on the pituitary gland so that cyclic activity resumes, and in most cases, progesterone is used. However, hormones that cause secretion of gonadotropins, or have a gonadotropic effect themselves can also be used for this purpose (Parkinson, 2019). Ovsynch has decreased efficiency in anoestrus cows than in cows with normal ovarian activity for several reasons: follicular response to the first GnRH is reduced, progesterone concentration is lower (partly because ovulation does not occur after the first GnRH, partly because endogenous CL is lacking in anoestrus cows) and there is a risk of a short luteal phase, even in cows where synchronous ovulation is achieved. Some modified pre-synchronisation protocols, such as G6G, have resulted in better conception rates in anoestrus cows then Ovsynch alone (Colazo and Mapletoft, 2014). The best results are obtained when Ovsynch is combined with progesterone devices, administered between days 0 and 7 of the Ovsynch protocol. Equine chorionic gonadotropin (eCG), can be administered concurrently with $PGF_{2\alpha}$ to better stimulate the growth of dominant follicles, especially in deep anoestrus cows (Bryan et al., 2013). This modification of progesterone supplemented Ovsynch has proven to be very efficient in anoestrus cows that are not in optimal body condition (Laven, 2019).

The second problem occurring in dairy cows is cystic ovarian disease (COD). Both GnRH and $PGF_{2\alpha}$ can be used for treatment of COD, depending on the type of the cyst (Parkinson, 2019). Therefore, Ovsynch can be used in treatment of COD (Nowicki et al., 2017). GnRH is expected to increase LH secretion from pituitary gland, resulting in luteinisation of cyst or in ovulation of new follicles. Sometimes, the cyst itself can rupture. The following $PGF_{2\alpha}$ administration results in lysis of luteal tissue. The second GnRH is expected to stimulate the follicles of previously induced follicular wave to ovulate, thus enabling FTAI of the treated animal. However, conception rates obtained after Ovsynch are not satisfying, and are 19%, as shown in Parkinson (2019). When Ovsynch modification, comprised of GnRH and $PGF_{2\alpha}$ on Day 0, $PGF_{2\alpha}$ on Day 14 and GnRH on Day 16, is used, results of oestrus detection, first AI conception rates and pregnancy rates obtained can be compared to those in healthy animals, and exceed those obtained with Ovsynch only (Gundling et al., 2015), with conception rates of 35% in modified Ovsynch and 19% in Ovsynch, respectively (Parkinson, 2019).

The second GnRH in Ovsynch can be replaced by human chorionic gonadotropin (hCG). DeRensis et al. (2008) observed a faster disappearance of ovarian cysts in this Ovsynch modification. Similar results were presented by other authors, indicating that this replacement could be a solution for improving Ovsynch efficiency for COD treatment, probably due to longer acting and better clinical effect of hCG compared to GnRH (Kinser et al., 1983). For treatment of luteal cysts, only $PGF_{2\alpha}$ can be used (Jeengar et al., 2014; Parkinson et al., 2019). In more than 80% of cows treated with $PGF_{2\alpha}$, the cysts disappear and oestrus occurs within 3 to 5 days after $PGF_{2\alpha}$ application (Dobson et al., 1977; Statham, 2016). The percentage of pregnant cows at first oestrus was 66% (Brito and Palmer, 2004). If the cow diagnosed with luteal cyst does not respond to $PGF_{2\alpha}$, it is most likely that the diagnosis was incorrect (Parkinson et al., 2019).

Conclusion

The implementation of hormonal protocols that enable oestrus synchronisation opens up many opportunities for reproductive management. The greatest advantage of certain protocols is the possibility of using AI at a predetermined time, which allows for less frequent handling of animals and improved time efficiency. An additional advantage of such protocols is the reduction of problems that occur when oestrus is not detected. Ovsynch is one of the most popular hormonal protocols based on the use of GnRH and $PGF_{2\alpha}$. This method is much more effective when used in cows than in heifers. In order to improve the pregnancy rates after the Ovsynch protocol, some modifications of the basic protocol are being investigated. Such modifications should address the problems that arise when developing follicles or corpus luteum do not respond to GnRH or $PGF_{2\alpha}$ application. Another drawback of the protocol that should be highlighted is the weak effect on the corpus luteum, but this could be overcome by using progesterone devices in the form of spirals or implants (Nowicki et al., 2017). In addition to routine cycle synchronization, the protocol can also be used in the treatment of ovarian cystic disease, silent heat, and heat stress.

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Ovsynch i njegove modifikacije u kontroli reprodukcije i liječenju određenih neplodnosti u mliječnih krava – kada i zašto?

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Ključne riječi: *mliječne krave, Ovsynch, presinkronizacija, resinkronizacija, GnRH,* $PGF_{2\alpha}$