Efficacy of progesterone supplementation during early pregnancy in cows: a meta-analysis

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Abstract

Progesterone is a critical hormone during early pregnancy in the cow. As a result a number of studies have investigated the effects of progesterone supplementation on pregnancy rates. In this study, a meta-analysis using a univariate binary random effects model was carried out on 84 specific treatments reported in 53 publications involving control (n=9905) and progesterone-treated (n=9135) cows. While the results of individual studies showed wide variations (-40 to +50 percentage point changes), progesterone treatment resulted in an overall increase in pregnancy rate (OR = 1.12; P<0.01). Improvements in pregnancy rate were only observed in cows treated at natural estrus (OR = 1.41, P<0.01) and not following synchronization of estrus or ovulation. While treatment between days 3-7 post-insemination was beneficial (OR = 1.15; P<0.01) treatment earlier or later than this was not. Progesterone supplementation was beneficial in cows of lower fertility (< 45% control pregnancy rate) but not in cows with higher fertility. These results indicated that the benefit of progesterone supplementation on fertility of cows required exogenous progesterone supplementation to start between day 3-7 and the appropriate reproductive status (i.e. lower fertility, natural estrus) of the treated cows.

Key words

Progesterone supplementation; Cow; Pregnancy; Meta-analysis

1. Introduction

Over the past few decades reproductive efficiency of dairy cows has continually declined. For example, Royal *et al.* [1] reported a fall in pregnancy rates to first service of approximately 1% per year in the UK, coupled with a dramatic increase in the incidence of reproductive problems. Over a similar period the rate of decline in the USA was around 0.5% per annum [2]. This trend has continued with Hudson *et al.* [3] reporting declining pregnancy rates between 2000 and 2006 across 250 UK herds.

An important factor contributing to early pregnancy failure is embryo mortality; early embryo loss due to the failure of maternal recognition of pregnancy is thought to account for up to 25-30% of pregnancy failures in dairy cows [4, 5]. The establishment of a successful pregnancy in the cow requires the embryo developing sufficiently to produce adequate amounts of the anti-luteolytic protein, interferon tau (IFNT) to prevent luteolytic $PGF_{2\alpha}$ secretion from the endometrium. One of the principal hormones in controlling pregnancy establishment is progesterone, which stimulates the production of endometrial secretions that are beneficial for the successful development of the embryo and subsequently survival [6, 7]. Insufficient circulating progesterone concentration has been clearly linked to poor embryo development and failure to prevent the development of the luteolytic signal in dairy cows [8]. Problems associated with the physiological mechanisms underpinning the establishment of pregnancy continue to compromise the reproductive performance of dairy cows.

In the past 60 years, the importance of progesterone to embryonic development has resulted in a plethora of studies that have attempted to improve pregnancy rate through post-insemination progesterone treatment. However, the results of published studies have failed to deliver any clear consensus on the therapeutic benefits of such treatments. While a number of studies have reported progesterone supplementation as beneficial, other studies have shown no benefit or even a marked reduction in pregnancy rate (e.g. [4, 5]). Overall, despite the fact that progesterone has a major influence on the outcome of pregnancy in the dairy cow and its widespread use, the reason for these different outcomes is still not clear and requires further study. The objective of this study was to assess the efficacy of progesterone supplementation in improving pregnancy rates of cows, by conducting a meta-analysis of data from all available progesterone administration studies.

2. Materials and methods

2.1 Identification of studies and inclusion criteria

All English-language papers and abstracts that published the results of studies investigating the efficacy of direct progesterone supplementation on pregnancy rates in cattle were identified by literature search (Web of Science, PubMed, Science Direct and Google Scholar) using the combination of keywords “progesterone” and “cattle” or “cow”. Studies included in the analysis needed to meet the criteria of being carried out in dairy or beef cows or heifers, reporting reproduction outcomes in sufficient detail for analysis and containing an appropriate control group. Published data in journal papers were crosschecked with conference papers to avoid repetition of data.

Extensive literature searches revealed a total of 55 papers and abstracts reporting studies where direct progesterone supplementation had been undertaken during early pregnancy (treatment started prior to day 21) in cattle. Two studies were excluded as one had no control group [9] and another because treatment was started after pregnancy had been diagnosed [10]. The remaining 53 papers (Appendix A), reporting 84 specific progesterone therapies applied to a total of 9135 treated cows, were then analyzed.

2.2 Summary of experimental animals and approaches represented in the analysis

Papers were published between 1953 and 2014 and reported studies carried out in 16 different countries in Asia, Europe, Oceania, North and South America. Data extracted from studies included number of treated and control cows, conception or pregnancy rates, treatment protocol (start and end day of progesterone treatment, administration method), pre-mating and mating protocol (mated at natural estrus or synchronized estrus or synchronized ovulation). Progesterone was administered as range of natural and synthetic progesterone and assorted progestagens by a variety of routes of administration (intravaginal, oral or injection). Treatment was started between days 0 (estrus) and 14 with a range of single, repeated and continuous treatment approaches. Across the various studies, treatment was ended on as early as day 0 and as late as day 34. While a number of reported studies did not specify the types of animals treated, in those that did treatment was administered to both beef and dairy cows / heifers and to both lactating and non-lactating animals. Once again, while some studies made no reference to the reproductive status of the experimental animals, in those that did, animals were classified as "fertile" or "sub fertile" or "repeat breeders" though the definitions used were not consistent and, for the purpose of the present analysis, conception rate in the control group was used to define reproductive status of the experimental animals in a particular trial. While many of the studies were carried out before the discovery of cycle synchronization technologies with mating at natural estrus, in more recent studies, a number of trials utilized either cycle synchronization protocols or, in some more recent studies full synchronization of ovulation coupled with fixed time AI. For the purpose of the present analysis, the term pregnancy rate was used to define the successful establishment of a pregnancy. However, it should be noted that, where specifically stated, pregnancy diagnosis took place at a range of times between days 25 and 100 following insemination.

2.3 Classification of studies for analysis

Three separate analyses were undertaken. In the first analysis, studies were classified according to the mating protocol:

- natural estrus
- synchronized estrus
- synchronized ovulation

In the second analysis, studies were classified according to the time that treatment was initiated in relation to anticipated physiological endogenous progesterone phases. These were:

- prior to the post ovulatory progesterone rise (< day 3)
- during the post ovulatory progesterone rise (day 3 to 7)
- following the post ovulatory progesterone rise (> day 7)

In the third analysis, studies were classified according to the conception rate of the experimental animals in the control group giving categories of:

- very poor (< 30%)
- poor (30.1 to 45%)
- good (45.1 to 60%)
- very good (> 60.1%)

Furthermore, in the classification groups in which positive results were identified and where the necessary information was provided, analysis of the influence of both type of progesterone used (progesterone or progestogen) and route of administration (vaginal or injection) was carried out. A comparison of type of cow (dairy or beef) was not possible due to low numbers of appropriate beef animal treatments.

2.4 Statistical analysis

All meta-analyses were conducted on the extracted number of pregnant/non-pregnant outcomes from all studies selected for inclusion using OpenMeta [Analyst] (Center for Evidence-Based Medicine, Brown University, USA). The I^2 statistic (degree of heterogeneity) was calculated by the Q statistic [11], which described the percentage of total variation across studies that was due to heterogeneity rather than chance. Where Q is the χ^2 heterogeneity statistic and k is the number of trials, I^2 is calculated as

$$I^2(\%) = \frac{Q-(k-1)}{Q} \times 100 \qquad [1]$$

A value greater than 50% can be considered substantial heterogeneity. The meta-analysis of all 84 studies revealed significant heterogeneity between studies (I^2 = 46%; $P < 0.01$). Thus, sources of heterogeneity were investigated by meta-regression which screened individual factors such as (1) start day of progesterone treatment; (2) pre-mating and mating protocol (estrus or synchronized estrus or synchronized ovulation) and (3) conception rate of the control group. Following this, the significant factors were analyzed in a univariate binary random effects (REML [restricted maximum likelihood]) model. Forest plots were created to present the odds ratio (OR) and their 95% confidence intervals (CI) of each analysis in a graphic manner. Each study was represented by a black box and a horizontal line, corresponding to the point estimates and the 95% CI of the individual study. The size of the box in the forest plot indicates the contribution of the study to the overall effect. Pooled OR estimates (and their 95% CI) was denoted by diamonds at the bottom of the same plot.

3. Results

3.1 Overall variation in the change of pregnancy rate associated with treatment

Figure 1 summarized overall variation in the change of pregnancy rate in all included 84 studies. The progesterone treatment resulted in a very wide variation of change of pregnancy rate (between -40 to + 50 percentage points). A total of 51 treatments numerically increased pregnancy rate, while it was decreased in 32 treatments and 1 treatment had no effect. An overall analysis of these studies showed a moderate, though highly significant, increase in pregnancy rate of 1.2 percentage points and an overall weighted mean (adjusted for trial size) increase of 2.5 percentage points following progesterone supplementation.

3.2 Effect of mating regime

Overall, treatment with progesterone resulted in a significant increase in the chance of a successful pregnancy (OR 1.12; P < 0.01). In studies conducted on cows mated at natural estrus, there was an increased chance of pregnancy (OR = 1.41; P < 0.01) with pregnancy rate increasing from 49.7% in control cows to 54.5% in treated cows (Fig 2). However, there was no improvement in pregnancy rate in cows treated following mating at either synchronized estrus (OR = 1.03) or synchronized ovulation (OR = 0.99).

3.3 Effect of time of treatment

The analysis of data from studies in which progesterone was administered before day 3 post-insemination, revealed an overall numerical reduction in the chance of pregnancy (OR = 0.87). It should be noted that in this category there was a particularly wide variation in response between studies (95% CI: 0.40 to 1.92) (Fig 3). Thus, while some treatments did increase the chance of pregnancy, these were outweighed by studies in which pregnancy rate was dramatically reduced. When progesterone treatment was initiated between day 3 to 7 following insemination period, there was an increase in the chance of pregnancy (OR = 1.15; P<0.01). However, treatment with progesterone after day 7 resulted in no significant change in pregnancy rate (OR= 1.04; P = 0.57).

3.4 Effect of initial conception rate

As shown in Figure 4, treatment of cows with low control pregnancy rates resulted in significant increases in the chance of pregnancy (< 30%: OR = 2.26, P < 0.01; 30 to 45%: OR=1.16, P<0.01). However, treatment of cows with relatively good initial pregnancy rates (> 45%) did not result in any improvement in pregnancy rate and, in cows with a pregnancy rate of 45 to 60% there was in fact a significant fall in pregnancy rate (OR = 0.87; P = 0.02).

There a total of 26 studies that treated cows with poor fertility (control pregnancy rate < 45%) with progesterone starting between day 3 to 7 following mating at natural estrus. In these studies, the chance of pregnancy was consistently increased by treatment (OR = 1.84; 95% CI = 1.47 to 2.30; P < 0.01).

3.5 Effect of treatment type

There was no difference in the effect of route of progesterone administration between injection (n = 18 studies; OR = 1.54; 95% CI = 1.08 to 2.22; P=0.018) and vaginal (n=19 studies; OR = 1.39; 95% CI = 1.08 to 1.78; P=0.012) administration with both giving similar responses. Similarly, no differences were found between administration of progesterone or various progestogens.

4. Discussion

The knowledge that progesterone has a major influence on the outcome of pregnancy in the cow, controlling the development of both the embryo and the luteolytic mechanism has led to numerous studies examining the effects of progesterone supplementation on pregnancy rate. However, the results of these studies vary wildly and so, in the present study, meta-analysis using data from relevant publications was conducted to clarify the efficacy of post-insemination progesterone supplementation on the pregnancy rate of cows.

Investigation of the influence of different pre-mating protocols on the efficacy of progesterone supplementation revealed significant benefits in cows mated at natural estrus but no effect in cows mated at synchronized estrus or following ovulation synchronization programs. It is likely that at least part of the delayed post-ovulatory progesterone rise may result from a loss of synchrony between the developmental stimulus required by the embryo and the timing of the post-ovulatory progesterone rise necessary to support that developmental stimulus. It is possible that in synchronized cycles, at least some of this asynchrony is avoided thus reducing the opportunity to rectify deficient progesterone support and deliver increases in pregnancy rate. Interestingly, while supplementation following cycle synchronization led to a numerical (though not significant) increase in pregnancy rate, supplementation following ovulation synchronization resulted in a numerical decrease in pregnancy rate, perhaps suggesting that this approach may more effectively negate the opportunity to improve pregnancy rate through progesterone supplementation.

Following mating at natural estrus, this asynchrony could also result from mistiming of actual insemination though any substantial mistiming of insemination around natural estrus would result in a failure of pregnancy beyond the help of progesterone supplementation.

While progesterone supplemented in the very early luteal phase, prior to day 3 post-insemination, had no overall beneficial effect on pregnancy rate, the results of individual trials fluctuated widely from large improvements to large reductions in pregnancy rate. Interestingly, earlier studies carried out in the 1950’s showed improvements while more recent studies were consistently detrimental. In both cattle and sheep, administration of progesterone early in the luteal phase to advance the post-ovulatory progesterone rise shortens the estrus cycle [12, 13] demonstrating the ability of the early progesterone rise to control the timing of subsequent luteolysis. Thus it is likely that early progesterone treatment can advance the onset of luteolysis to a point in time before which the embryo is able to muster an adequate antiluteolytic response. It has been demonstrated that a plasma concentration of progesterone of as low as 0.6 $ng.ml^{-1}$ was sufficient to trigger a premature luteolytic signal in most cows [14]. One explanation for the efficacy of the studies carried out in the 1950's may be that the potency of the progesterone treatments administered were insufficient to achieve this threshold and may have exerted positive effects on the embryo while not advancing luteolysis. However, it is clear that, in the modern cow, very early supplementation can be very detrimental as it led to an overall reduction in pregnancy rate from 44.3 to 37.4 %.

A significant portion of reduced fertility in the cow is attributable to inadequate maternal luteal function and inadequacies in the progesterone dependent uterine environment [8]. It was not unexpected, therefore, that in contrast to the very early treatment, progesterone treatment during the first week (days 3-7) of pregnancy, during the period of the post ovulatory progesterone, rise resulted in a significant increase in pregnancy rate. Progesterone supplementation during the early stages of embryonic development, at the time of onset of the postovulatory progesterone rise, is likely to induce a uterine environment more conducive to embryonic development and in such cows, rescue some of the delayed embryos and thereby improve the conception rate. However, treatment initiated after day 7 did not improve pregnancy rate. Mann, Fray [15] reported improvements in embryo development and IFNT production following progesterone administration from day 5 to 9 after AI but not following treatment from days 12 to 16. Thus it appears that, once the post ovulatory progesterone rise has occurred, further exogenous progesterone has no additional benefit to the developing embryo or to the outcome of pregnancy.

When investigating the impact of conception rate of control cows on the efficacy of progesterone supplementation on pregnancy rate, a positive response to progesterone supplementation was only found in cows with relatively low fertility (conception rate < 45%), while supplementing progesterone to cows with relatively good initial conception rates (> 45%) did not result in any benefit. This low fertility may result from poor ovulation, inappropriately timed estrus or simply insufficient endogenous circulating progesterone to support the survival of the early embryo. A lower total progesterone concentration has been measured in low-fertility cows after estrus [16]. Thus, cows with relatively good fertility probably already have adequate progesterone for embryo growth and subsequent signaling of pregnancy to the cow. In such situations the scope of progesterone supplementation to 'rescue' the pregnancy is limited.

5. Conclusions

The results clearly demonstrate that the administration of progesterone treatment too early (< day 3) or too late (> day 7) or to cows with relatively good reproductive performance delivers no benefit in terms of pregnancy rate. Furthermore, treatment of cows following cycle or ovulation synchronization is also ineffective. However, the results have clearly demonstrated a consistent increase in the chance of pregnancy in animals of relatively poor fertility supplemented with any form of progesterone by any route of administration during the period of the post ovulatory progesterone rise (day 3 to 7) following mating at natural estrus.

Conflict of interest

The authors confirm that they have no conflicts of interest to declare.

Authors' contribution

Leyan Yan collected the data and drafted the manuscript. Robert Robinson performed the statistical analysis. George Mann designed the study and helped to draft the manuscript. Zhendan Shi participated in the design of the study. All authors read and approved the final manuscript.

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Appendix A References included in the meta-analysis:

Authors	Year	Country	Type of cattle	Mating regime	Type of progestagen	Route	Reference
Alnimer & Lubbadeh	2008	Jordan	Dairy cows	TAI	Progesterone	Vaginal	[17]
Amiridis *et al.*	2009	Greece	Dairy cows	Estrus	Progesterone	Vaginal	[18]
Arndt *et al.*	2009	Canada	Dairy cows	TAI	Progesterone	Vaginal	[19]
Awasthi *et al.*	2002	India	Cows	Estrus	Progestagen	Injection	[20]
Beltman *et al.*	2009	Ireland	Beef heifers	Synchronized	Progesterone	Vaginal	[21]
Colazo *et al.*	2013	Canada	Dairy cows	TAI	Progesterone	Vaginal	[22]
Dawson	1954	-	-	Estrus			[23]
Denson *et al.*	2005	USA	Dairy cows	Synchronized	Progesterone	Vaginal	[24]
Diskin & Sreenan	1986	Ireland	-	Estrus	-	-	[25]
Ferguson *et al.*	2012	USA	Beef (non-lactating)	Estrus	Progesterone	Injection	[26]
Forro *et al.*	2012	Germany	Dairy cows	TAI	Progesterone	Vaginal	[27]
Friedman *et al.*	2012	Israel	Dairy cows	Estrus	Progesterone	Vaginal	[28]
Ghasemzadeh *et al.*	2006	Iran	Dairy cows	Estrus	Progesterone	Vaginal	[29]
Hanlon *et al.*	2005	New Zealand	Dairy cows	Synchronized	Progesterone	Vaginal	[30]
Herrick	1953	-	Heifers	Estrus	-	-	[31]
Inderjeet *et al.*	2000	India	Cows	Estrus	Progestagen	Injection	[32]
Jimenez *et al.*	2013	Mexico	-	Estrus	Progesterone	Injection	[33]
Johnson *et al.*	1958	USA	Dairy cows & heifers	Estrus	Progesterone	Injection	[34]
Kendall *et al.*	2009	UK	Dairy	Estrus	Progesterone	Vaginal	[35]
Khoramian *et al.*	2011	Iran	Dairy cows	Estrus	Progesterone	Vaginal	[36]
Kumar *et al.*	2009	India	-	Estrus	Progestagen	Injection	[37]
Kumar *et al.*	2012	India	Dairy cows	Estrus	Progestagen	Injection	[38]
Lang *et al.*	2012	Germany	Dairy cows	Synchronized	Progesterone	Vaginal	[39]
Larson *et al.*	2007	USA	Dairy cows	Estrus	Progesterone	Vaginal	[40]
Long *et al.*	2010	Japan	Dairy cows	TAI	Progesterone	Vaginal	[41]
Lynch *et al.*	1999	New Zealand	Dairy heifers	Synchronized	Progesterone	Vaginal	[42]
Macmillan & Peterson	1993	New Zealand	Dairy cows	Estrus	Progesterone	Vaginal	[43]
Mann *et al.*	1998	UK	Dairy cows	Estrus	Progesterone	Vaginal	[44]
Marques *et al.*	2014	Brazil	Dairy cows	TAI	Progesterone	Vaginal	[45]
Mehni *et al.*	2012	Iran	Dairy cows	Estrus	Progesterone	Vaginal/Injection	[46]
Monteiro *et al.*	2014	USA	Dairy cows	Synchronized/TAI	Progesterone	Vaginal	[47]
Munro & Bertram	1990	Australia	Beef cows	Synchronized	Progesterone	Vaginal	[48]
Nascimento *et al.*	2010	USA	Dairy cows	TAI	Progesterone	Vaginal	[49]
Parr *et al.*	2014	Ireland	Dairy cows	Estrus	Progesterone	Vaginal	[50]
Rhodes *et al.*	2001	New Zealand	Dairy cows	Synchronized	Progesterone	Vaginal	[51]
Robinson *et al.*	1989	Canada	Dairy cows	Estrus	Progesterone	Vaginal	[52]
Shams-Esfandabadi & Shirazi	2007	Iran	Dairy	-	Progestagen	Injection	[53]
Shams-Esfandabadi *et al.*	2011	Iran	Dairy cows	Estrus	Progesterone	Vaginal	[54]
Singh *et al.*	2002	India	Dairy	Estrus	Progestagen	Injection	[55]
Singh *et al.*	2008						[56]
Sreenan & Diskin	1983	Ireland	-	Estrus	-	-	[4]
Srivastava *et al.*	2001	India	-	Estrus	Progestagen	Injection	[57]
Starbuck *et al.*	2001	UK	Dairy cows	Estrus	Progesterone	Vaginal	[58]
Sterry *et al.*	2005	USA	Dairy	TAI	Progesterone	Vaginal	[59]

Stevenson & Mee	1991	USA	Dairy cows	Synchronized	Progesterone	Vaginal	[60]
Stevenson *et al.*	2007	USA	Dairy cows	Synchronized	Progesterone	Vaginal	[61]
Thielen *et al.*	2006	USA	Beef	TAI	Progesterone	Vaginal	[62]
Thuemmel *et al.*	1992	USA	Dairy cows & heifers	Estrus	Progestagen	Injection	[63]
Van Cleeff *et al.*	1991	USA	Dairy heifers	Synchronized	Progesterone	Vaginal	[64]
Van Cleeff *et al.*	1996	USA	Dairy heifers	Synchronized	Progesterone	Vaginal	[65]
Villarroel *et al.*	2004	Spain	Dairy cows	Estrus	Progesterone	Vaginal	[66]
Walton *et al.*	1990	Canada	Dairy cows	Estrus	Progesterone	Vaginal	[67]
Wiltbank *et al.*	1956	USA	Dairy cows	Estrus	Progesterone	Injection	[68]

Figure Legends

Fig 1: Summary diagram illustrating the overall variation in the change of pregnancy rate associated with progesterone treatment in 84 experimental studies included in current meta-analysis. The vertical lines show the changes in pregnancy rate after post-insemination progesterone supplementation in individual study. A total of 51 treatments increased, 32 treatments decreased pregnancy rate, and 1 treatment has no effect resulting in an overall mean increase in pregnancy rate of 1.2 percentage points.

Fig 2: Odds ratios (OR) and 95% confidence intervals (CI) of studies investigate the effect of progesterone treatment on pregnancy rate of cows undergone different pre-mating programs. Black boxes are the mean OR for progesterone treatment on pregnancy rate from each study and their area is proportional to the contribution of the study to the overall analysis. The diamond at the bottom represents pooled OR estimates and on the right of the solid vertical line represents the positive effect of progesterone treatment on pregnancy rate. The overall OR (1.41) of studies conducted on estrus cows indicated that progesterone supplementation had a beneficial effect on fertility ($P<0.01$). While, for the cows which received synchronized estrus protocol or timed artificial insemination (TAI), the pregnancy rate was not improved by administration of progesterone (OR = 1.03 and 0.99, respectively).

Fig 3: Odds ratios (OR) and 95% confidence intervals (CI) of studies investigating the effect of start time of treatment on the efficacy of progesterone supplementation in pregnancy rate of cows. Black boxes are the mean OR of progesterone treatment on pregnancy rate from each study and their area is proportional to the inverse variance of the estimates in the pooled analysis. The diamond at the bottom represents pooled OR estimates and on the right of the solid vertical line represents the positive effect of progesterone treatment on pregnancy rate.

Initiation of progesterone supplementation during the period of 3-7 days following insemination significantly improved the fertility of cows (OR = 1.15, $P < 0.01$). While, very early (before days 3) and too late (> day 7) progesterone treatment has no beneficial effect on pregnancy rate of cows ($P > 0.05$).

Fig 4: Odds ratios (OR) and 95% confidence intervals (CI) of studies investigate the effect of progesterone on the pregnancy rate of cows with different initial conception rate. Black boxes are the OR of progesterone treatment on pregnancy rate from each study and their area is proportional to the inverse variance of the estimates in the pooled analysis. The diamond at the bottom represents pooled OR estimates and on the right of the solid vertical line represents the positive effect of progesterone treatment on pregnancy rate. The results demonstrated that progesterone supplementation have benefit on cows of relatively poor fertility (conception rate ≤ 45 %) ($P < 0.01$), and no beneficial effect on cows with relatively good reproductive performance (conception rate > 45 %) (OR < 1).

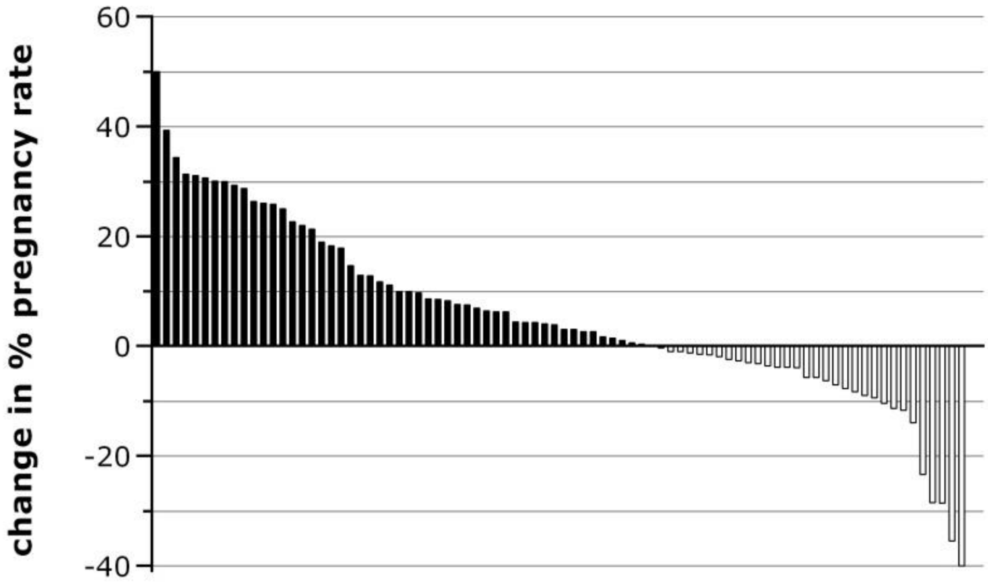

Fig 1. Summary diagram illustrating the overall variation in the change of pregnancy rate associated with progesterone treatment in 84 experimental studies included in current meta-analysis.

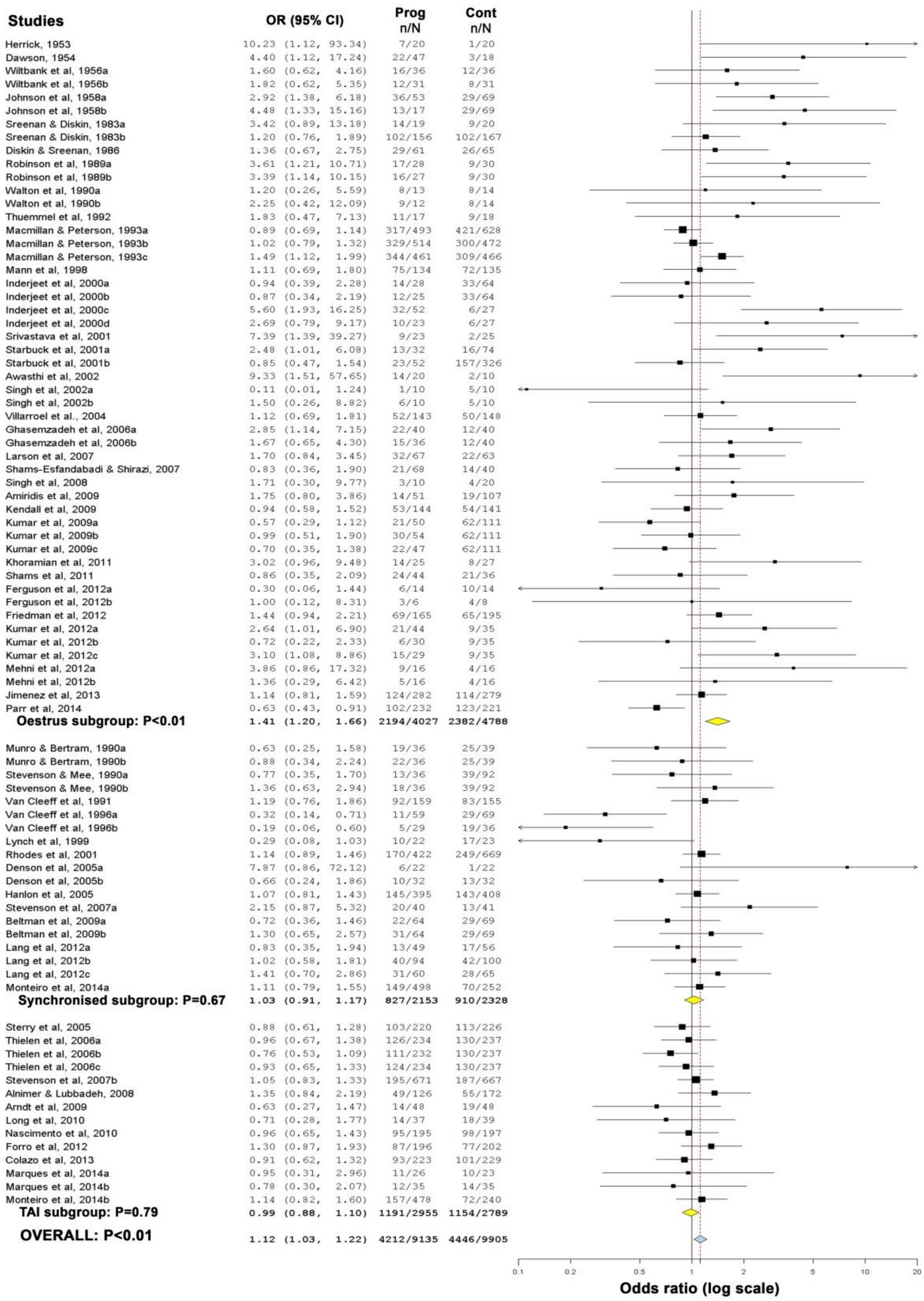

Fig 2. Odds ratios (OR) and 95% confidence intervals (CI) of studies on the effect of progesterone treatment on pregnancy rates of cows undergoing different pre-mating programs.

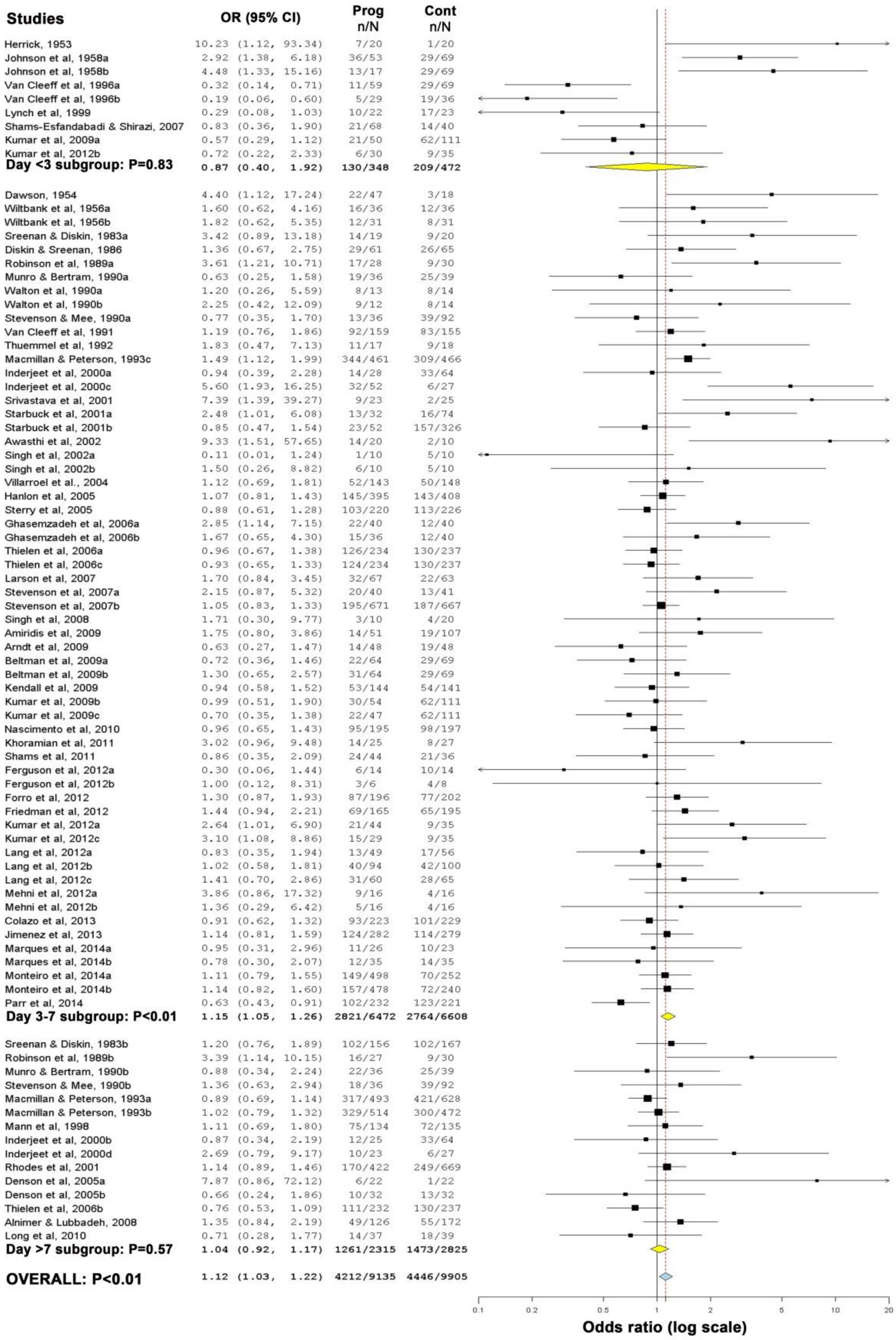

Fig 3. Odds ratios (OR) and 95% confidence intervals (CI) of studies investigating the effect of time of treatment on the efficacy of progesterone on pregnancy rate of cows.

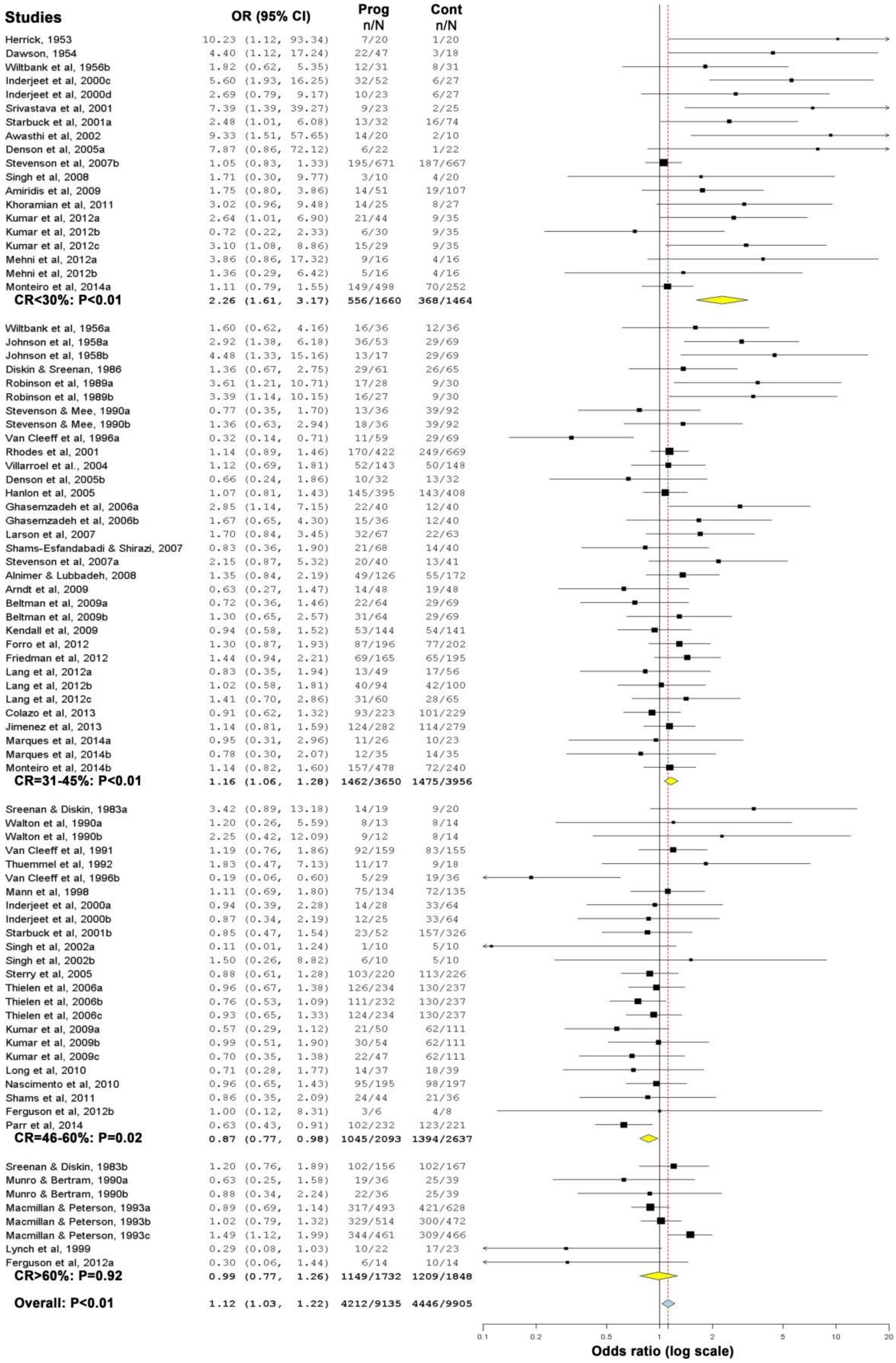

Fig 4. Odds ratios (OR) and 95% confidence intervals (CI) of studies investigating the effect of initial conception rate on efficacy of progesterone treatment on the pregnancy rate of cows

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