

Scientific Article

A Bayesian meta-analysis of the effects of administering an intra-vaginal (CIDR) device in combination with other hormones on the reproductive performance of cycling, anoestrous and inseminated cows

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Abstract

AIMS: To evaluate the effectiveness of treatment programmes that included controlled internal drug-releasing (CIDR) devices containing progesterone (P4) in improving synchrony of oestrus, and conception and pregnancy rates in cycling, anoestrous and inseminated dairy cows, using meta-analysis. To describe the difference in response between cycling and anoestrous cows to CIDR-based synchrony programmes.

METHODS: Scientific papers written in the English language between 1989 and 2002 that investigated the effects of treatment programmes including CIDR devices on reproductive performance in dairy heifers or lactating dairy cows were identified using a computerised literature search. The criteria for inclusion incorporated evidence that treatment allocation was completely randomised; the population studied was lactating dairy cows; and that data were available on submission, conception and pregnancy rates and their associated measures of variability. Reproductive outcomes from 25 synchrony trials (total n=11,058 cows) were analysed. Summary measures of the effect of treatment on reproductive outcome were assessed using fixed- and random-effects Bayesian meta-analysis models.

RESULTS: Treatment programmes including a CIDR device increased the risk of submission in cycling cows (predicted Bayesian RR=2.86, 95% credible interval=1.46–5.67). Compared with controls, synchrony programmes including CIDR devices in cycling dairy cows had no effect on the risk of conception to first service post-treatment (predicted Bayesian RR=1.00, 95% credible interval=0.80–1.24). Compared with controls, synchrony programmes including CIDR devices had no effect on the risk of pregnancy throughout the mating period (predicted Bayesian RR=1.02, 95% credible interval=0.89–1.17). In anoestrous cows, CIDR treatment had no effect on the risk of conception to first service post-treatment and no effect on the risk of pregnancy throughout the mating period, compared with anoestrous, untreated controls (predicted Bayesian RR=0.91 and 0.97, respectively; 95% credible interval=0.68–1.26 and 0.59–1.60, respectively).

CONCLUSION: The results of this meta-analysis showed that synchrony programmes using CIDR devices combined with other hormones reliably enhanced submission rates in lactating dairy cows. The relatively small number of trials with data

suitable for analysis and the heterogeneity of results at the individual trial level limited our ability to confirm either a beneficial or deleterious effect of treatment on conception or pregnancy rates. Further randomised, controlled trials to evaluate the effectiveness of this form of reproductive therapy in commercial dairy farms are needed.

KEY WORDS: *Bayesian meta-analysis, CIDR, anoestrus, oestrus, synchronisation, progesterone, dairy cattle, reproduction*

Introduction

A predictably strong ovulatory response during a specified 12–24 h period and high pregnancy rates to a single breeding after treatment are the critical requirements for effective synchronisation of oestrus in cattle. Despite increasing knowledge of ovarian follicular development (Ginther et al 1996), these two requirements have not been met successfully to date. Research in the early 1960s showed that P4 treatments of >14 days duration resulted in good synchrony of oestrus but low pregnancy rates (Macmillan and Peterson 1993). Subsequently, the treatment period was reduced to 9–12 days by administration of oestradiol as a luteolytic agent at the start of the progestagen treatment (Wiltbank and Kasson 1968; Roche 1974). While this procedure resulted in improved pregnancy rates, there was greater variability in the onset of oestrus compared with protocols that used longer periods of P4 exposure (Roche et al 1999).

Progesterone was the hormone originally used in attempts to synchronise the bovine oestrous cycle (Lamond 1964; Gordon 1976). In those studies, animals received daily injections of the steroid in varying amounts for up to 20 days. These treatments resulted in acceptable synchrony but low fertility. Subsequent developments focussed on the oral, injectable or transdermal use of potent synthetic progestagens (Hansel 1967; Jöchle 1972). Further advances using P4 coincided with the development and systematic testing of the P4-releasing internal device (Webel 1976). This intra-vagi-

CI	Confidence interval(s)
CIDR	Controlled internal drug-releasing
df	Degrees of freedom
GnRH	Gonadotropin-releasing hormone
MCMC	Markov chain Monte Carlo
ODB	Oestradiol benzoate
PGF _{2α}	Prostaglandin F _{2α}
P4	Progesterone
RR	Relative risk(s)
SE	Standard error

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nal device was used on its own, or in combination with oestradiol benzoate (ODB) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (Roche 1974, 1976; Roche et al 1981). Despite achieving average plasma P4 concentrations >1.5 ng/ml to suppress endogenous luteinising hormone release (Roche et al 1981), the degree of variation in P4 concentration among individually treated animals was not studied (Macmillan and Peterson 1993). In the past decade, CIDR devices containing 1.9 g P4 have been widely used for oestrous synchrony in dairy cattle. Trials and reviews have been conducted to assess the usefulness of CIDR devices for manipulation and control of reproduction in cattle (Macmillan and Peterson 1993). There is a great body of information on the efficacy of synchrony programmes that include CIDR devices, but most studies conducted to date fail to provide consistent evidence of an improvement in overall reproductive performance, or lack sufficient data on fertility criteria.

The aims of the present meta-analysis of randomised controlled trials were: to evaluate the effectiveness of treatment programmes that included CIDR devices in improving synchrony of oestrus, and conception and pregnancy rates, in dairy heifers or lactating dairy cows; and to describe the difference in response between cycling and anoestrous cows to CIDR-based synchrony programmes.

Materials and methods

Papers written in the English language between 1989 and 2002 that investigated the effect of the intra-vaginal P4-releasing device, CIDR (InterAg, Hamilton, NZ), in combination with other hormones on oestrous cycle synchrony and pregnancy rates in dairy heifers and lactating dairy cows were identified using a computerised literature search (CAB, BA abstracts, PubMed and ScienceDirect), library searches of relevant journals, and a review of citations in identified review papers. Authors of research on CIDR-based synchrony programmes were contacted to obtain published information not identified by other search methods.

For this study, the outcomes of interest were: (1) submission rate, defined as the proportion of cows that had an oestrus event detected and were submitted for service in the 7-day period following removal of the device; (2) conception rate, defined as the proportion of inseminations that resulted in a confirmed pregnancy; and (3) pregnancy rate, defined as the proportion of treated or control cows that became pregnant within a specified period after the start of mating.

Trials included / excluded in the study

A total of 203 trials were considered for analysis. Trials were considered eligible for analysis on the basis of criteria developed and specified by the first two authors. These criteria included satisfactory evidence that: (1) treatment allocation was randomised; (2) the population studied comprised dairy heifers or lactating dairy cows; and (3) data were available on submission, conception and pregnancy rates and their associated measures of variability. Ineligible trials included: 53 non-randomised controlled clinical trials; 30 trials in which positive controls were treated with CIDR devices or other forms of P4; 25 trials in which supplementary treatments were given; 13 trials in which non-lactating cows were used; 10 trials in which the subjects were beef rather than dairy animals; and 47 trials in which insufficient data were available for analysis. Details of the final set of eligible trials ($n=25$) are pre-

sented in Tables 1 and 2. Published data in peer-reviewed papers were cross-checked with conference papers to avoid duplication of information.

Extracted data

Data extracted from each trial included the number of cows enrolled in treatment and control groups, submission rates, first service conception rates, and final pregnancy rates for cycling and anoestrous cows. Conception rate data were also extracted from trials that used CIDR devices to supplement P4 during the first 2 weeks post-insemination. Other information extracted included whether or not negative (no treatment) or positive (treatment with other medication) controls were used, and details of the treatment protocol including the dose and route of administration of gonadotropin-releasing hormone (GnRH), ODB, and $PGF_{2\alpha}$ at insertion or removal of the CIDR device.

Statistical analysis

Submission rates, first service conception rates, and overall pregnancy rates for treatment and control groups in each trial were used to calculate the crude relative risk (RR) of submission, conception, and/or pregnancy following treatment. Variations among RR at the trial-level were assessed using a chi-squared test of heterogeneity. In this case, the null hypothesis was that the effect of treatment was the same across k trials, which was rejected if the heterogeneity test statistic was greater than a critical value that separated the upper 10% of a χ^2 distribution with $(k-1)$ degrees of freedom (df). In this case, an α -level of 0.10 was used on account of the relatively poor power of the chi-squared test to detect heterogeneity among small numbers of trials (Egger and Davey Smith 2003).

To estimate the effect of CIDR-based treatment on reproductive outcome, Bayesian meta-analysis models were used (Domenici et al 1999). Here, the observed number of events in the control group of each trial, O_i^C , was assumed to be from a binomial distribution defined by parameters π_i^C (representing the underlying probability of a positive reproductive outcome in the control group) and n_i^C (representing the number of subjects in the control group). The observed number of events in the treatment group, O_i^T , was similarly defined by parameters π_i^T and n_i^T , in Equation 1:

$$O_i^C \sim \text{binomial}(\pi_i^C, n_i^C)$$

$$O_i^T \sim \text{binomial}(\pi_i^T, n_i^T)$$

Using a fixed-effect Bayesian approach, we assumed that the log of the RR of a positive reproductive outcome following treatment, $\log(\pi_i^T/\pi_i^C)$, followed a normal distribution with mean θ and variance proportional to the number of subjects enrolled in the trial. Within the Bayesian paradigm, an uninformed normal prior centred at zero was assigned to θ .

To account for heterogeneity among trial results, a random effects Bayesian approach was used in which the log of π_i^C was assumed to be a function of individual trial-level effects, λ_i , and the log of π_i^T assumed to be a function of individual trial-level and treatment effects ($\lambda_i + \theta_i$), in Equation 2:

$$\log \left\{ \frac{\pi_i^T}{\pi_i^C} \right\} = \frac{\lambda_i + \theta_i}{\lambda_i}$$

In this case, the effect of treatment, θ_i , was parameterised as having a normal distribution with mean μ and variance τ^2 . This allowed the effect of treatment observed across the i trials (θ_i) to

vary around a 'true' mean (μ) with variance τ^2 . An uninformed normal prior centred at zero was used for μ and an uninformed inverse gamma distribution used for τ^2 (Best et al 2000). An uninformed normal prior centred at zero was assigned to the individual trial-level effect parameter, λ_i .

To estimate values of the various parameters, a joint probability distribution was formed by combining the prior distributions with the likelihood, given the observed data. Markov chain Monte Carlo (MCMC) methods implemented within the WinBUGS software package (Spiegelhalter et al 1999) were used to obtain samples from the joint posterior distribution to estimate θ (in the case of the fixed-effects models) and μ and τ^2 (in the case of the random-effects models). Our aim was to provide summary meas-

ures of treatment effect relevant to clinical decision making; thus, in addition to reporting the credible intervals of the RR estimates for the fixed- and random-effects models, summary measures of effect have been reported as the 95% credible intervals of the RR estimates derived from μ and τ^2 . In practical terms, this predicted distribution should be thought of as the RR estimate of a successful reproductive outcome when a CIDR-based programme is used in a future (or unobserved) trial (Parmigiani 2002).

For the Bayesian analyses, the MCMC sampler was run for 40,000 iterations and the first 1,000 'burn in' samples were discarded. Convergence of the posterior sampling distribution was visually assessed using cumulative path plots and quantified using the Raftery and Lewis convergence diagnostic (Raftery and Lewis

Table 1. Duration of treatment with a controlled internal drug-releasing (CIDR) device and dose of gonadotropin-releasing hormone (GnRH), oestradiol benzoate (ODB), prostaglandin (PG), pregnant mare serum gonadotropin or no hormones (N/A) administered before or after insertion and removal of the CIDR device in cycling and anoestrous lactating dairy cows.

Authors	Trial No.	Duration of CIDR treatment (days)	Treatment protocol		
			Before insertion of CIDR	Day of insertion of CIDR ^c	Before/after removal of CIDR
Cycling cows					
Day et al (2000)	1	7	ODB injection (1 mg)	63	PG
	2	7	ODB injection (2 mg)	63	PG
Rhodes et al (2001)		7	ODB injection (2 mg)	>21	PG
Xu and Burton (1998)		12	ODB capsule (10 mg)	>28	ODB injection (1 mg)
Xu and Burton (2000)	1	8	GnRH (10 μ g)	-	PG
	2	7	GnRH (10 μ g)	-	PG
Xu et al (1997a) ^a		5	PG (pre-synchrony)	-	PG
Anoestrous cows					
Clark et al (1999)	1	6	N/A	>21	ODB injection (1 mg)
	2	6	N/A	>21	ODB injection (1 mg)
Hanlon et al (2000)		6	N/A	>30	ODB injection (1 mg)
Jubb et al (1989)		7	N/A	-	PMSG (400 IU)
		7	N/A	-	PMSG (400 IU)
McDougall et al (2001) ^b		6	N/A	>20	ODB injection (1 mg)
Xu et al (1997b)		5	ODB capsule (10 mg)	-	ODB injection (1 mg)

^a Positive control (prostaglandin F_{2 α})

^b Positive control (Ovsynch)

^c Day post-calving

Table 2. Days of insertion of a controlled internal drug-releasing (CIDR) device after artificial insemination (AI), duration of treatment (days), and type of device (new vs used) in lactating dairy cows which received supplementary progesterone after insemination.

Authors	Day of insertion of CIDR after AI	Duration of CIDR treatment	Type of CIDR
Davis et al (1992) ^a	6	11	New
Davis et al (1992) ^a	6	11	New
Davis et al (1992) ^a	6	11	New
Larson et al (1995) ^a	3	7	Used
Macmillan and Peterson (1993)	14-17	4-7	New
Macmillan and Peterson (1993)	10-16	6	New
Macmillan and Peterson (1993)	4-9	6 or 12	New
Mann et al (2001)	10	7	Used
Van Cleef et al (1996)	1	8	New
Van Cleef et al (1996)	1	8	Used
Van Cleef et al (1991)	7	6	Used
Van Cleef et al (1991)	7	6	Used

^a Conference papers

1992ab). Posterior sample sizes were determined by running sufficient iterations to ensure that the Monte Carlo standard error (SE) of the posterior means were at least one order of magnitude smaller than their posterior standard deviation (Best et al 2000). Parallel chains of the MCMC sampler were run using diverse initial values to ensure that convergence was achieved to the same distribution (Gelman 1996).

Sensitivity to the distributional assumptions was assessed by assuming different distributions for the trial effects and comparing subsequent inferences. For example, a second series of analyses were conducted where the variance of treatment effect (τ^2) was assumed to arise from a uniform distribution. Within a model, we determined how sensitive the combined estimate was to any one trial. This was achieved by leaving one trial out, calculating the combined effect of the remaining trials, and comparing the results with the combined effect based on all trials.

Results of each model were summarised as forest plots. For these, each study was represented by a black square and a horizontal line, corresponding to the point estimate and the 95% confidence interval (CI) of the individual trial-level RR. Pooled RR estimates (and their 95% credible intervals) for the fixed-effects, random-effects, and prediction models were denoted by diamonds on the same plot.

Publication bias

Funnel plots (Light and Pillemer 1984) were constructed to identify publication bias. Estimates of precision, in this case the log of the RR of a positive reproductive outcome following treatment, of individual trials were plotted on the horizontal axis and sample size on the vertical axis. The nature of the sample distribution meant that each plot would be naturally funnel-shaped with an apex pointing upwards. If publication bias was present, the plot would have a deficiency, usually in the area occupied by small negative trials. This technique was based on the premise that the precision in estimating the treatment difference would increase as the sample size of the trial increased (Whitehead 2002).

Results

This study examined a total of 25 trials in cycling and anoestrous cows and heifers, and in cows for which P4 supplementation was used during the post-insemination period (n=11,058 cows). Summaries of the pooled RR of submission, conception, and pregnancy rates are shown in Table 3.

Among the eligible trials, few reported measures of time-from-calving or start-date-of-mating-to-pregnancy, or treatment-to-conception intervals, and none reported any measure of variability (e.g. SE of the mean), therefore these data could not be pooled to calculate the effect of treatment. Where papers provided results from different farms or series of studies, these were considered as separate trials. In some cases, information was only extracted from the first or second round of synchrony programmes.

Figure 1 presents the outcomes in six trials that evaluated the effect of CIDR-based synchrony programmes on submission rate in cycling, lactating dairy cows. Although there was significant heterogeneity among the results of these trials ($\chi^2=54.6$, $df=5$; $p<0.01$), CIDR-based synchrony programmes were associated with RR estimates greater than unity in all cases. Compared with the controls, treated cows were 2.86 times more likely to be submitted to service following treatment (predicted Bayesian RR=2.86, 95% credible interval=1.46–5.67).

Seven trials reported first-service conception rates in cycling, lactating treated and control cows without heterogeneity among trial results ($\chi^2=10.08$, $df=6$; $p=0.12$). Synchrony programmes including CIDR devices in cycling, lactating dairy cows had no effect on the risk of conception to first service (predicted Bayesian RR=1.00, 95% credible interval=0.80–1.24; Figure 2). There was no evidence of heterogeneity among the six trials reporting the effect of CIDR-based synchrony programmes on overall pregnancy rate ($\chi^2=6.63$, $df=5$; $p=0.25$). Compared with controls, synchrony programmes including CIDR devices had no effect on the risk of pregnancy throughout the mating period (predicted Bayesian RR=1.02, 95% credible interval=0.89–1.17; Figure 3).

Table 3. Summary of tests of heterogeneity and summary estimates of treatment effect for a meta-analysis of studies investigating the effect of controlled internal drug-releasing (CIDR) treatment on reproductive outcomes in cycling and anoestrus cows.

Groups analysed	Status	Heterogeneity	df	P-value	Predicted Bayesian relative risk (95% credible interval)	Variance of trial-specific treatment effect (95% credible interval) ^a
Submission rate	Cycling	54.60	5	<0.01	2.86 (2.21–3.73)	0.06 (0.01–0.38)
Sensitivity test		3.91	4	0.41		
Conception to 1st service	Cycling	10.08	6	0.12	1.00 (0.80–1.24)	0.01 (0.00–0.04)
Sensitivity test		6.80	5	0.24		
Overall pregnancy	Cycling	6.63	5	0.25	1.02 (0.89–1.17)	0.00 (0.00–0.01)
Sensitivity test		2.40	4	0.66		
Conception to 1st service	Anoestrous	8.53	6	0.20	0.91 (0.68–1.26)	0.01 (0.00–0.09)
Sensitivity test		4.01	5	0.54		
Overall pregnancy	Anoestrous	5.29	2	0.07	0.97 (0.59–1.60)	0.01 (0.00–0.40)
Sensitivity test		0.07	1	0.79		
Conception rate	P4 post-insemination	32.10	11	<0.01	1.02 (0.59–1.64)	0.03 (0.00–0.24)
Sensitivity test		13.72	9	0.13		

^a Variance of trial-specific treatment effect (τ^2)
df = degrees of freedom; P4 = progesterone

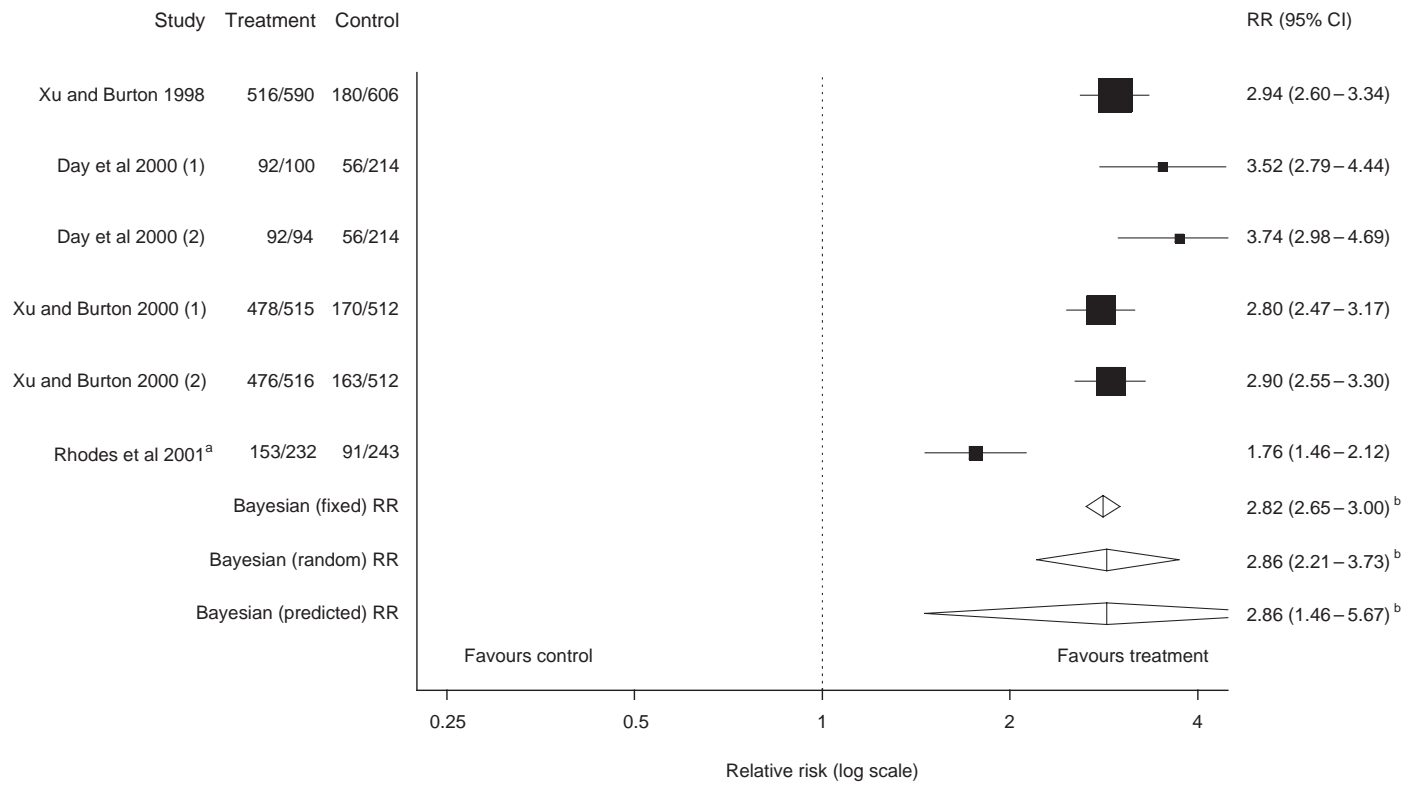


Figure 1. Relative risks (RR) (and their 95% confidence intervals, CI) determined from the results of six trials comparing submission rates in cycling cows treated with controlled internal drug-releasing devices or placebo. Box sizes are relative to the total number of animals in each trial. Summary estimates of treatment effects are shown using: (1) a Bayesian (fixed-effects) approach; (2) a Bayesian (random-effects) approach; and (3) the predicted distribution of RR estimates expected in a future trial.

Test of heterogeneity: $\chi^2=54.6$, $df=5$; $p<0.01$

^a Test of heterogeneity following exclusion of study: $\chi^2=3.94$, $df=4$; $p=0.41$

^b 95% credible interval

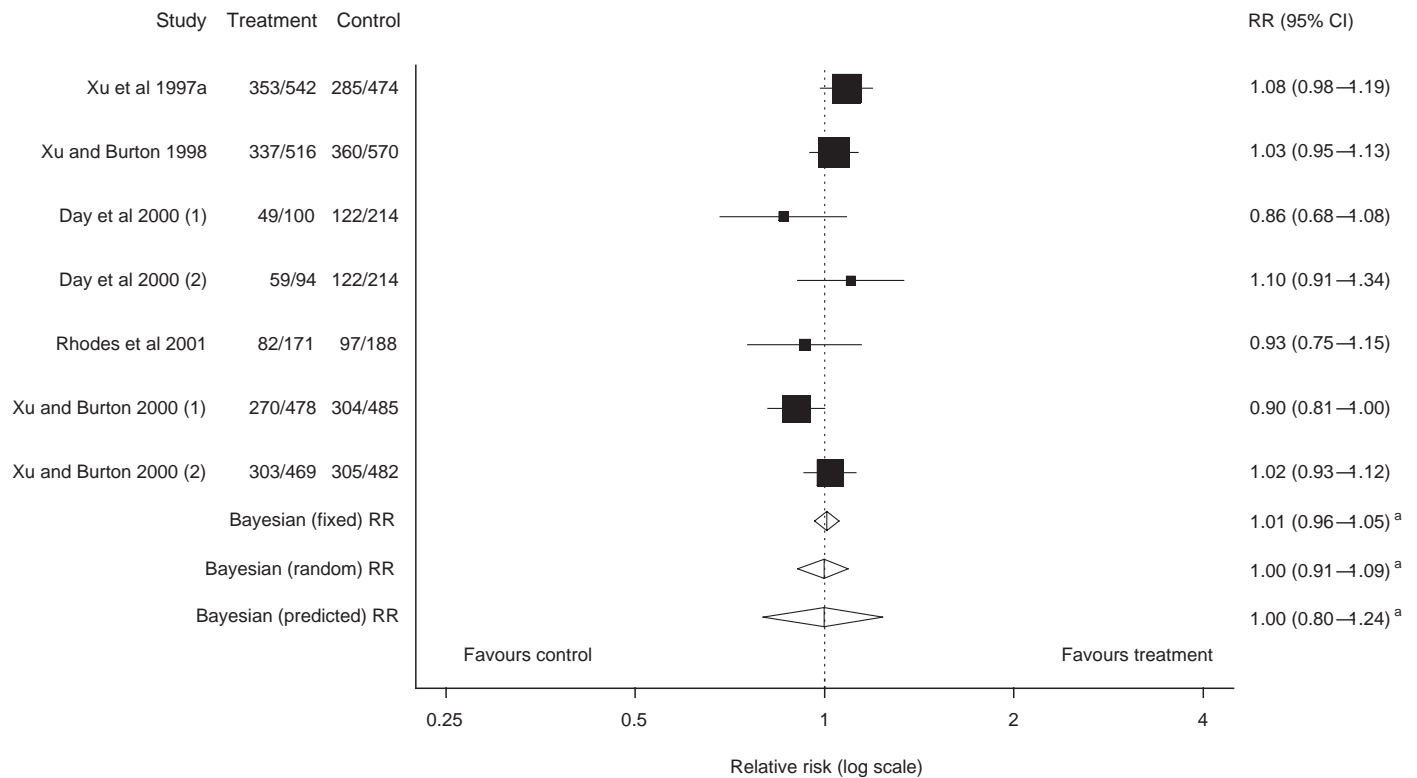


Figure 2. Relative risks (RR) (and their 95% confidence intervals, CI) determined from the results of seven trials comparing first service conception rates in cycling cows treated with controlled internal drug-releasing devices or placebo. Box sizes are relative to the total number of animals in each trial. Summary estimates of treatment effects are shown using: (1) a Bayesian (fixed-effects) approach; (2) a Bayesian (random-effects) approach; and (3) the predicted distribution of RR estimates expected in a future trial.

Test of heterogeneity: $\chi^2=10.08$, $df=6$; $p=0.12$

^a 95% credible interval

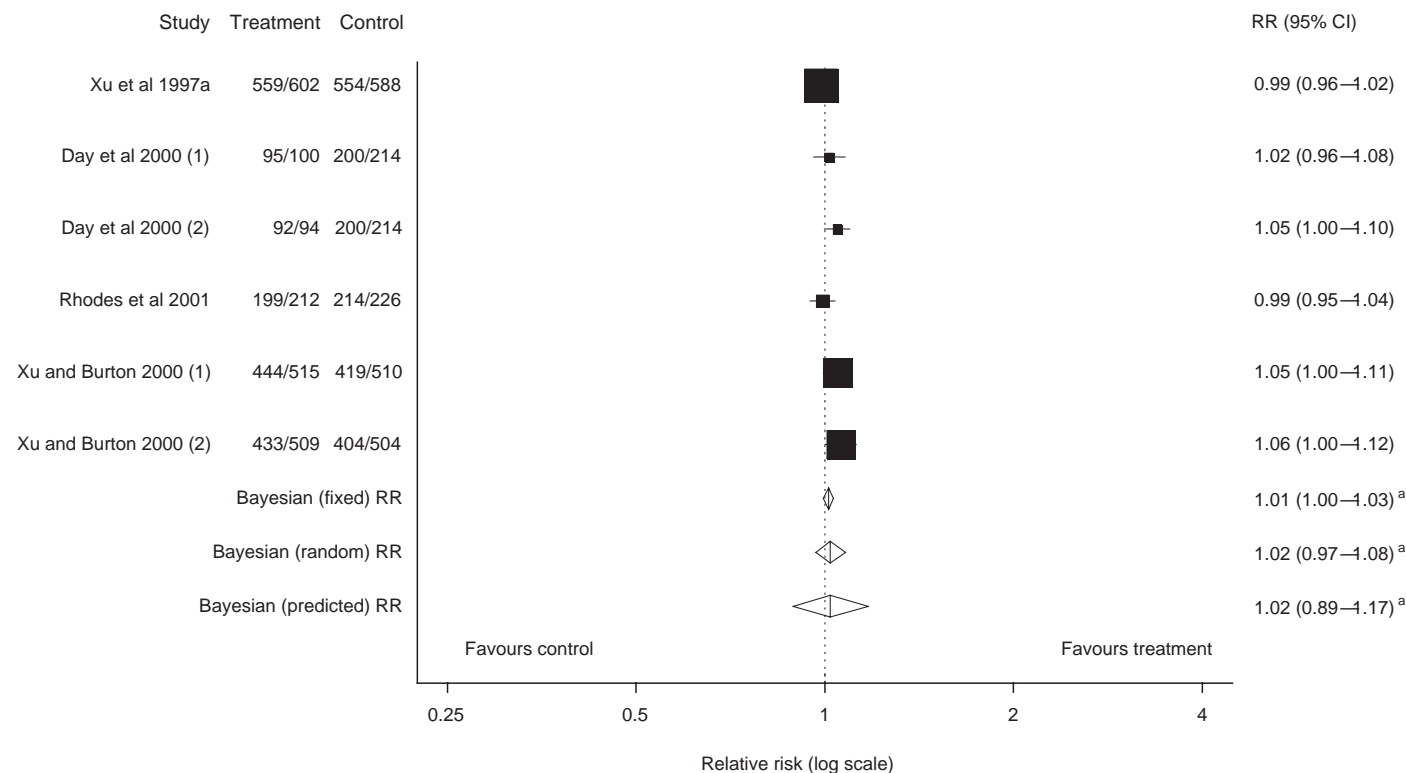


Figure 3. Relative risks (RR) (and their 95% confidence intervals, CI) determined from the results of six trials comparing overall pregnancy rates in cycling cows treated with controlled internal drug-releasing devices or placebo. Box sizes are relative to the total number of animals in each trial. Summary estimates of treatment effects are shown using: (1) a Bayesian (fixed-effects) approach; (2) a Bayesian (random-effects) approach; and (3) the predicted distribution of RR estimates expected in a future trial.

Test of heterogeneity: $\chi^2=6.63$, $df=5$; $p=0.25$

^a 95% credible interval

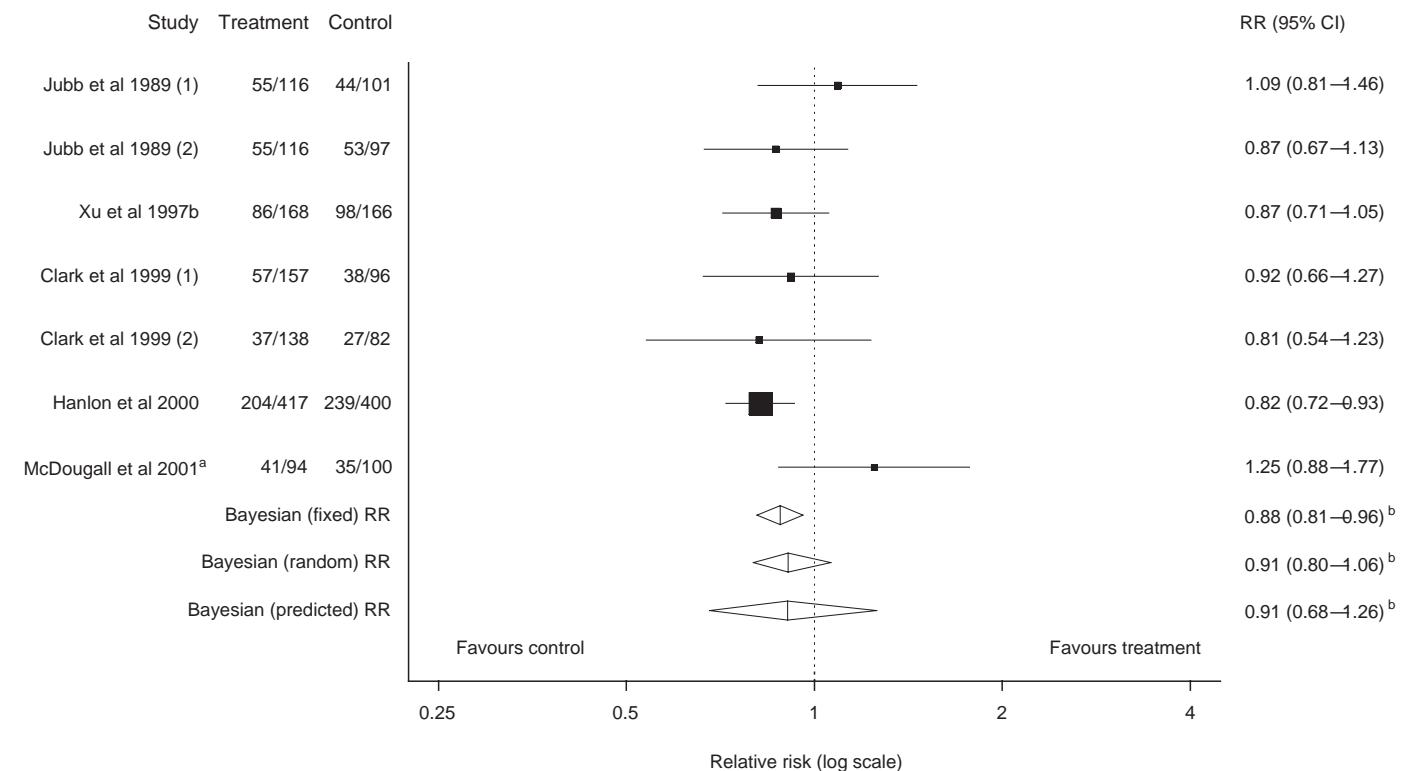


Figure 4. Relative risks (RR) (and their 95% confidence intervals, CI) determined from the results of six trials comparing first service conception rates in non-cycling cows treated with controlled internal drug-releasing devices or placebo. Box sizes are relative to the total number of animals in each trial. Summary estimates of treatment effects are shown using: (1) a Bayesian (fixed-effects) approach; (2) a Bayesian (random-effects) approach; and (3) the predicted distribution of RR estimates expected in a future trial.

Test of heterogeneity: $\chi^2=8.53$, $df=6$; $p=0.20$

^a Test of heterogeneity following exclusion of study: $\chi^2=4.07$, $df=5$; $p=0.54$

^b 95% credible interval

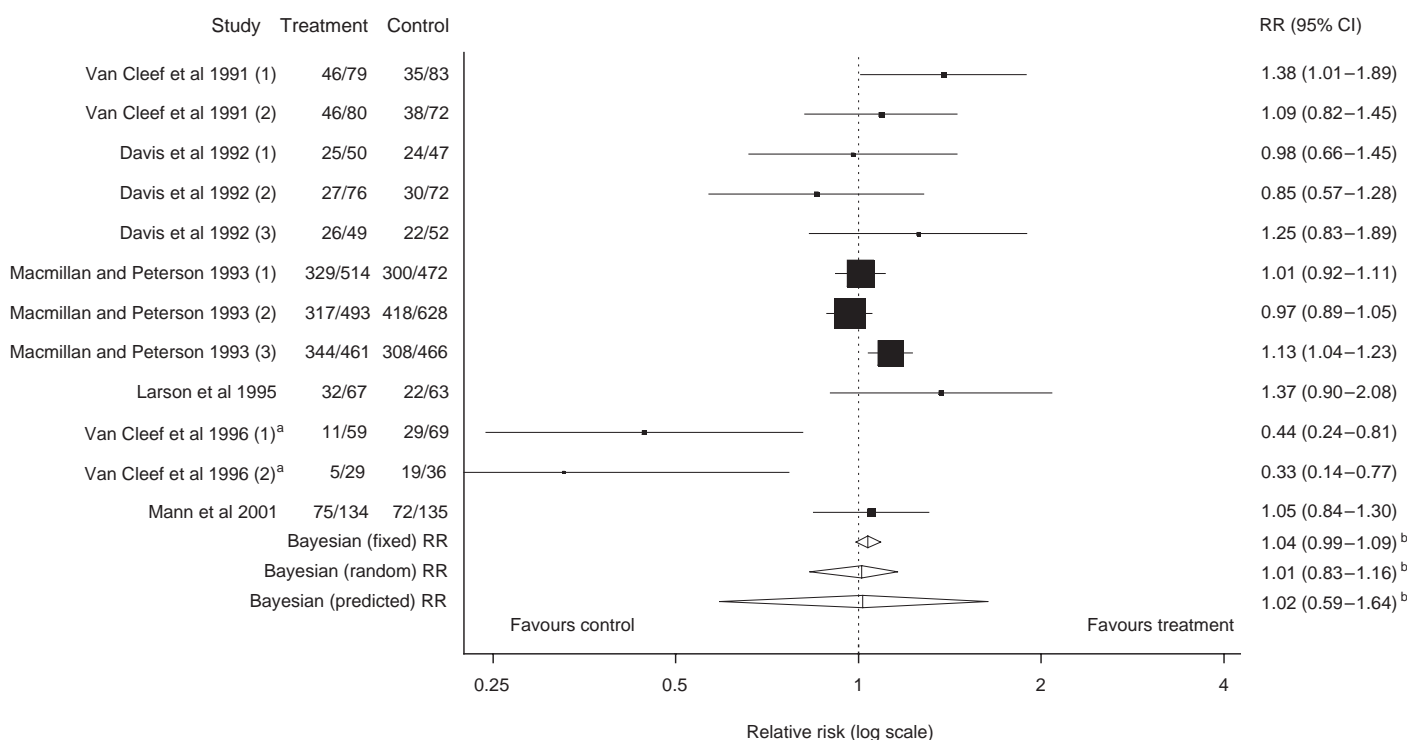


Figure 5. Relative risks (RR) (and their 95% confidence intervals, CI) determined from the results of twelve trials comparing pregnancy rates in cows treated post-insemination with controlled internal drug-releasing devices or placebo. Box sizes are relative to the total number of animals in each trial. Summary estimates of treatment effects are shown using: (1) a Bayesian (fixed-effects) approach; (2) a Bayesian (random-effects) approach; and (3) the predicted distribution of RR estimates expected in a future trial.

Test of heterogeneity: $\chi^2=32.10$, $df=11$; $p<0.01$

^a Test of heterogeneity following exclusion of studies: $\chi^2=13.72$, $df=9$; $p=0.13$

^b 95% credible interval

Seven trials involving lactating, anoestrous dairy cows compared the effect of CIDR-based synchrony treatment with controls on first service conception rate and showed no evidence of heterogeneity ($\chi^2=8.53$, $df=6$; $p=0.20$; Figure 4). In anoestrous cows, CIDR-based synchrony programmes had no effect on the risk of conception to first service post-treatment, compared with anoestrous, untreated controls (predicted Bayesian RR=0.91, 95% credible interval=0.68–1.26). Significant heterogeneity existed among the three trials evaluating the effect of synchrony treatment on overall pregnancy rate ($\chi^2=5.29$, $df=2$; $p=0.07$). In anoestrous cows, CIDR-based synchrony programmes had no effect on the risk of pregnancy throughout the mating period, compared with anoestrous, untreated controls (predicted Bayesian RR=0.97, 95% credible interval=0.59–1.60).

Twelve post-insemination P4-supplementation trials were used in the meta-analysis of conception rate data (Figure 5). Results from these trials were heterogeneous ($\chi^2=32.10$, $df=11$; $p<0.01$). There was no overall effect of P4 supplementation post-insemination on risk of conception (Bayesian RR=1.02, 95% credible interval=0.59–1.64) compared with untreated controls. Following exclusion of the two trials of Van Cleef et al (1996), there was no evidence of heterogeneity among the 10 other trials ($\chi^2=13.72$, $df=9$; $p=0.13$). There was no significant difference in conception rate between trials that used new compared with used CIDR devices. The insertion of a CIDR device before or after Day 7 post-insemination did not alter the risk of pregnancy in cows.

Funnel plots constructed to identify publication bias in the data on CIDR-based synchrony programmes were not able to detect any bias, due to the small number of papers eventually included in this study (results not shown).

Discussion

This study used meta-analytical methods to summarise results from a series of trials that studied the potential applications of CIDR-based synchrony programmes in the manipulation and control of reproduction in dairy cattle. Only 25/203 (12%) trials identified by a comprehensive literature search provided sufficient data to enable aspects of reproductive performance (submission, conception and pregnancy rates) to be quantified. Although cost is a significant factor that influences the adoption of any new form of reproductive technology, it is not the sole factor. Elements of convenience, the opportunity to save time and labour, and the potential of the technology to improve time to submission and conception are other critical factors which must also be considered. Meta-analyses are a useful aid for this type of decision making, allowing results of a series of trials to be combined to provide an overall summary of effect, and allowing animal treatment options to be evaluated on a more objective basis. Determining the degree of similarity or difference between the results of apparently similar trials, and examination of possible sources of variability, are primary issues in the conduct of a meta-analysis (Greenland 1994; Olkin 1994). Consequently, we examined sources of heterogeneity in the study results presented.

In cycling cows, submission rates were significantly greater in synchronised cows than those in control groups (predicted Bayesian RR=2.86, 95% credible interval=1.46–5.67). Heterogeneity in the results of reported submission rates was influenced by the results of Rhodes et al (2001), in which there was a notable difference in measurement of the outcome variable; the reproductive response to treatment was a detectable corpus luteum rather than an ob-

served oestrus event. A sensitivity analysis conducted following exclusion of that trial showed that the results of the remaining trials were homogenous and, when combined, produced an increase in the risk of submission, compared with placebo-treated controls (predicted Bayesian RR=3.09, 95% credible interval=2.25–4.42). These data showed that synchrony programmes using CIDR devices in combination with other hormones reliably increased the probability of submission, offering herd managers the potential to reduce costs associated with detection of oestrus, labour, artificial breeding, and pregnancy diagnosis. These outcomes are important in seasonally calving dairy herds in which breeding and calving are planned to optimise pasture intake and milk production (Xu and Burton 1998, 2000; Rhodes et al 2001).

The analyses presented in this study show that CIDR-based synchrony treatment of cycling cows had little or no effect on the risk of conception to first service or overall risk of pregnancy (Figures 2 and 3, respectively). Early attempts to synchronise oestrus in cattle using P4 (Trimberger and Hansel 1955) were based on the knowledge that P4 prevents the occurrence of oestrus and ovulation (Christian and Casida 1948). It has been documented that most synchronisation programmes involving progestagens are associated with a reduction in conception rate at the synchronised oestrus (Odde 1990; Larson and Ball 1992; Ryan et al 1995). However, other trials reported improvement in the fertility of cows following intra-vaginal P4 treatment for a period of ≤ 12 days (Roche 1976; Smith et al 1984). Rosenberg et al (1990) and Wehrman et al (1993) reported that P4 supplementation during the luteal phase prior to insemination resulted in higher conception rates.

Amongst anoestrous cows, neither conception rates to first service nor overall pregnancy rates differed between treated and untreated control cows. However, the small number of trials for which pregnancy rate data suitable for analysis were available ($n=3$) precluded our ability to draw definitive conclusions from this comparison.

Several factors contribute to the probability of reproductive failure in anovulatory cows. There is some evidence that cows in poor body condition and negative energy balance are more likely to be anovulatory (Burke et al 1998). An anovulatory period for at least the first 3 weeks postpartum has been reported in seasonal dairy herds in New Zealand (Fielden et al 1973; McDougall et al 1995) and this period was extended for primiparous cows and those with a low body condition score at calving (Grainger et al 1982; McDougall et al 1995). A prolonged postpartum anovulatory period was a major factor affecting the reproductive performance of dairy cows in pasture-fed, seasonally calving herds (Xu and Burton 1996). The interval from calving to first ovulation was longer for cows under those systems compared with cows fed rations that included concentrate supplements (Butler and Smith 1989; Savio et al 1990; McDougall et al 1995; Xu and Burton 1996). As a result, a large proportion of cows in pasture-fed, seasonally calving dairy herds may have been anoestrous at the start of a given breeding season (Xu et al 2000). The results of our analysis, albeit based on the results of only three trials, support a hypothesis that the use of a P4-based treatment programme may not be sufficient to resolve fertility problems if feeding strategies are inadequate.

Previous meta-analyses have identified a positive effect of post-insemination P4 supplementation on pregnancy rate. A review by Royal et al (2000) reported results of a meta-analysis claiming

a 5–10% improvement in fertility following post-insemination P4 treatment. However, those authors did not provide sufficient details of their analytical methods to enable critical evaluation, details of the dose and form of P4 used, the number of cows enrolled in eligible trials, or definition of fertility outcomes, making it difficult to verify their findings. A review by Mann and Lamming (1999) summarised the results of a number of studies undertaken in a variety of cattle populations and environments using various P4 supplementation methods post-insemination. Those authors reported that pooled data showed a significant improvement in fertility following P4 supplementation. However, their conclusion appears flawed since no attempt appears to have been made to account for between-study heterogeneity in the data. Both Royal et al (2000) and Mann and Lamming (1999) noted that P4 supplementation might improve pregnancy rates in herds in which pregnancy rates were low. It is possible that these comments may reflect the statistical phenomenon of regression to the mean (Newell and Simpson 1990) rather than the physiology underlying the effect.

Our analyses showed that CIDR treatment of cows after insemination did not improve overall pregnancy rates (predicted Bayesian RR=1.02, 95% credible interval=0.59–1.64; Figure 5). Heterogeneity among the results of trials included were influenced by the results of two trials involving heifers (Van Cleef et al 1996), in which the RR of pregnancy was low in treated cows (RR=0.33, 95% CI=0.14–0.77 (Trial 1), and RR=0.44, 95% CI=0.24–0.81 (Trial 2); Figure 5). There was a notable difference in the design of these two trials, as the insertion of CIDR devices was performed on Day 1 after insemination, compared with Days 3–10 in the other trials in the group. Sensitivity analysis, excluding the trials of Van Cleef et al (1996), showed that the results of the remaining studies were homogenous. Normal early embryonic development and pregnancy were found to be associated with high P4 levels initiated on Days 4–10 post-insemination (Erb et al 1976; Hansel 1981; Maurer and Echternkamp 1982; Lamming et al 1989; Albihin et al 1991; Parkinson et al 1994; Larson et al 1995). The positive relationship between P4 and fertility in cows may be due to enhanced embryonic growth and development (Garrett et al 1988ab; Albihin et al 1991) in cows in which P4 levels increase more rapidly to a higher peak within the first 7 days post-ovulation. However, reports of the effectiveness of supplemental P4 treatments using different forms of P4, including CIDR devices, are variable as some trials identified a positive effect (Robinson et al 1989; Macmillan and Peterson 1993; Larson et al 1995), some a negative effect (Van Cleef et al 1996), and others no effect on pregnancy rate (Garrett et al 1988b; Van Cleef et al 1991). Much of this variation can be attributed not only to different sources and doses of exogenous P4 used (e.g. new *vs* used CIDR devices), but also to differences in timing and length of the supplementation period.

In conclusion, the response of dairy cows to CIDR-based synchrony programmes is influenced by their physiological state at the time of treatment, concurrent use of other reproductive hormones, and the duration of treatment. Given these factors, it is inevitable that there will be considerable variation in the results of individual trials. Although the random-effects meta-analytical methodology used in this study was able to account for these influences, the small number of trials from which data suitable for analysis were available resulted in relatively large predicted Bayesian credible intervals of RR, reducing the power of these analy-

ses to detect true treatment effects and our ability to draw more definite conclusions.

The results of this study showed that while treatment programmes using CIDR devices reliably enhanced submission rates, they did not influence first service conception rates or overall pregnancy rates. Thus, it demonstrates a need for further randomised controlled trials into the effectiveness of this form of reproductive therapy on commercial dairy farms. Data evaluating the time to pregnancy after calving or mating start dates, or treatment to conception intervals, would be especially valuable in assessing the economic merit of these reproductive technologies. We recommend that workers use survival methods to analyse these data and keep raw data for inclusion in future meta-analytical studies.

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