

1 **F & S 27600 decline and resubmit**

2 **Title:** Evaluation of progestogen supplementation for luteal phase support in fresh IVF  
3 cycles.

4 **Running title:** Evaluating luteal phase support.

5

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26 **Funding;** Amal Mohammed was funded by The Republic of Iraq, Ministry of Higher  
27 Education and Scientific Research.

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30 **Structured Abstract:**

31

32 **Objective:** To evaluate the effectiveness of progestogen supplementation in improving  
33 clinical pregnancy rates in women undergoing fresh IVF cycles and to compare different  
34 routes, start times, durations and estrogen co-administration regimen.

35 **Design:** Comprehensive systematic review and meta-analysis.

36 **Setting:** University.

37 **Patients:** Women undergoing fresh IVF cycles who did and did not receive progestogen  
38 supplementation.

39 **Intervention(s):** Summary odds ratios (ORs) were calculated by binomial logistic  
40 regression.

41 **Main Outcome Measure(s):** Clinical pregnancy rates.

42 **Results:** 82 articles (26,726 women) were included. Clinical pregnancy rates were  
43 increased by intramuscular (OR=4.57;  $p<0.001$ ), vaginal (OR=3.34;  $p<0.01$ ),  
44 subcutaneous (OR=3.36;  $p<0.01$ ) or oral (OR=2.57;  $p<0.05$ ) progestogen  
45 supplementation versus no treatment. Greatest benefit was observed when progestogens  
46 were supplemented intramuscularly versus vaginally (OR=1.37;  $p<0.001$ ). The optimal  
47 time to commence administration was between oocyte retrieval and embryo transfer  
48 (OR=1.31;  $p<0.01$ ), with oocyte retrieval +1 day being most beneficial. Co-administration  
49 of estrogen had no benefit (OR=1.33;  $p>0.05$ ) whether progestogens were co-  
50 administered vaginally or intramuscularly. Clinical pregnancy rates were equivalent when  
51 progestogen supplementation was ceased after  $\leq 3$  weeks or continued for up to 12 weeks  
52 (OR=1.06;  $p>0.05$ ).

53 **Conclusion:** This broad-ranging meta-analysis highlights the need to re-evaluate current  
54 clinical practice. The use of progestogens in fresh IVF cycles is substantially beneficial to  
55 clinical pregnancy. Critically, the use of intramuscular progestogens should not be  
56 dismissed, as it yielded the greatest clinical pregnancy rates. Pregnancy success was  
57 impacted by initiation of therapy, with one day after oocyte retrieval being optimal. There  
58 is little evidence to support co-administration of estrogen or prolonging progestogen  
59 treatment beyond three weeks.

60 **Keywords:** (3-5) meta-analysis, progestogen, estrogen, luteal phase support, fresh IVF

61 **Capsule:** Luteal phase deficiency commonly occurs after ovarian stimulation in women  
62 undergoing assisted reproduction. Progestogen supplementation is a routine and critical  
63 component for luteal phase support, however, the optimal regimen remains unresolved.

64

65

66 **Introduction**

67 Luteal phase deficiency is a common result of assisted reproductive technologies (ART)  
68 and is characterised by inadequate or inappropriate progesterone production. This  
69 inevitably compromises the successful establishment and maintenance of pregnancy, and  
70 has led to the critical requirement for luteal support protocols. Luteal phase deficiency has  
71 been attributed to diminished luteotrophic support from pituitary LH, reduced luteal  
72 steroidogenic capacity and/or premature luteolysis (1-3). Hence, the provision of  
73 exogenous progestogens to supplement endogenous progesterone production has become  
74 a routine component of ART.

75 In recent years, there has been much debate as to whether the immediate transfer of  
76 "fresh" embryos or cryopreservation with subsequent transfer of frozen embryos confers  
77 the greatest pregnancy success for patients (4, 5). Indeed, elective freeze-all cycles have  
78 been widely advocated and adopted (6), with an anticipated improvement in endometrial  
79 receptivity thought to give rise to an improved pregnancy outcome (7). However, recent  
80 evidence suggests that whilst a freeze-all strategy is of benefit to women who are highly  
81 responsive to ovarian stimulation, it is not beneficial for those women with a low or  
82 intermediate response (8). Therefore, there is an ongoing need for the evaluation of luteal  
83 phase support in fresh IVF cycles.

84 The potential supplementation regimens for luteal phase support following ART are  
85 numerous; progestogens are available in a number of formulations (of progesterone or  
86 synthetic progestins) and can be administered by nasal, rectal, vaginal, oral, subcutaneous  
87 or intramuscular routes alone, or via multiple routes in combination. Progestogen  
88 administration can commence before oocyte retrieval, on the day of oocyte retrieval or in  
89 the days soon afterwards, or on or around the day of embryo transfer. Supplementation  
90 can then be maintained for several weeks, until a positive urinary pregnancy test, until  
91 fetal heart pulsations have been observed or until week 12 of gestation or later (9). Luteal  
92 phase progestogens may also be co-administered with estrogen.

93 While there is an agreed need for luteal phase support following ART (10), the choice of  
94 preparation, route of delivery, time at which to commence treatment and its duration  
95 remain a matter of debate (11, 12). The wide variation in clinical approach means that the  
96 choice of luteal phase support for couples undergoing ART is far from clear. Evidence from  
97 clinical practice suggests a current global preference for luteal phase support via vaginal  
98 progestogens in tablet form, administered from the day of oocyte collection and  
99 maintained for 8-10 weeks (9).

100 The current study critically evaluates the efficacy of luteal phase support by analysing the  
101 impact of these complex treatment choices on pregnancy rates following fresh embryo

102 transfer via binomial logistic regression, with the aim of both influencing practice and  
103 providing an essential point of reference for patients. In contrast to previous meta-  
104 analyses, our use of binomial logistic regression enables the synthesis of results from the  
105 numerous studies performed without control groups. This distinctive and robust statistical  
106 approach has the benefit of greatly broadening both the scope of questions answered and  
107 the number of study groups eligible for each comparison (13). This includes addressing  
108 largely overlooked and important questions or those with few existing RCTs (14), such as,  
109 determining the optimal day on which to commence progestogen supplementation.

110 Recent commentary (11) has concluded that the luteal phase in ART is deserving of greater  
111 attention, such as provided by this analysis. Furthermore, whilst the clinical approach to  
112 luteal phase support may be becoming more consistent (9, 15), the suggested lack of  
113 evidence-based decision making (9) may ultimately limit pregnancy success or lead to  
114 women undergoing additional treatment for luteal phase support that is of little benefit.

## 115 **Methods**

116

### 117 *Search strategy*

118 An extensive systematic literature search was performed using Google Scholar  
119 <https://scholar.google.com/>, PubMed <https://www.ncbi.nlm.nih.gov/pubmed> and Web of  
120 Science <http://wok.mimas.ac.uk> (last accessed April 2018). Searches were performed in  
121 English and included studies (excluding abstracts and conference proceedings) published  
122 between 1980 and January 2018. For this purpose, the principal search terms in the title,  
123 abstract or keywords were "progesterone supplementation" OR "progestogen  
124 supplementation" OR "luteal support" in conjunction with "vaginal" OR "intramuscular" OR  
125 "oral" OR "subcutaneous" OR "rectal". A separate search was conducted with the following  
126 terms "assisted reproductive technology or ART", "in vitro fertilization or IVF", "intra-  
127 cytoplasmic sperm injection or ICSI", or "fresh embryo transfer". The references within  
128 these articles including any meta-analysis were scrutinised for any additional articles.  
129 These search results were subsequently combined to yield a total of 517 articles (excluding  
130 duplicates) (Supplementary Fig 1).

### 131 *Selection of articles: methodology and criteria*

132 Following the PRISMA guidelines (16), the title, abstract and keywords were screened to  
133 confirm that the article was within subject remit and this excluded 327 articles (e.g.  
134 animal models). Then, the full text of each manuscript was obtained and reviewed. For  
135 articles to be included, the following inclusion criteria were assigned: 1) included sub-  
136 fertile women (undefined or defined aetiology) undergoing ART with fresh embryo

137 transfer; 2) involved ovarian stimulation; 3) included an evaluation of pregnancy outcomes  
138 between two groups of women, either progestogen versus untreated control group, or  
139 comparing at least 2 different regimens of luteal support involving progestogen; 4)  
140 included pregnancy outcome represented as clinical pregnancy (e.g. presence of a  
141 gestational sac, with or without a fetal heartbeat on ultrasonography) as defined in the  
142 original manuscript.

143 Articles were excluded for the following reasons: 1) assignment of progestogen treatment  
144 occurred after a positive HCG pregnancy test, 2) the only luteal support was HCG  
145 treatment; 3) studies involved frozen or donor oocyte cycles. A total of 108 articles were  
146 excluded, resulting in 82 articles submitted to the meta-analysis (Supplementary Fig 1).

#### 147 *Assessing the risk of bias*

148 Two authors (RSR & KJW) independently assessed the risk of bias in each included article  
149 across several domains according to previous criteria (10); random sequence generation,  
150 allocation concealment, blinding of participants and personnel, blinding of outcome  
151 assessment, incomplete outcome data, selective reporting and other potential sources of  
152 bias (e.g. apparent variations in patient management or embryo quality between arms).  
153 Studies were classified as being at low, high or unclear risk of bias and the risk of bias  
154 analysis was used to generate a risk of bias summary figure (Supplementary Fig 2) and  
155 graph (Supplementary Fig 3).

156 In order to minimize any risk of bias across studies and in recognition of the difficulty of  
157 identifying publication bias and selective reporting, a comprehensive and broad-ranging  
158 systematic literature search for eligible studies was conducted. The articles were  
159 thoroughly interrogated for any duplication of data.

#### 160 *Data collection process*

161 Data extraction was performed independently by two reviewers (AM & RSR) and  
162 discrepancies were resolved by discussion with a third reviewer (KJW). The following data  
163 were extracted from each article: route of progestogen administration, dose of  
164 progestogen and duration of progestogen treatment, the time when progestogen  
165 supplementation commenced and the presence or absence of estrogen co-treatment.  
166 Clinical pregnancy was considered the primary pregnancy outcome, with additional data  
167 on live birth tabulated when given. Additional extracted information included  
168 country/region of origin, publication date, number of patients, mean age of participants,  
169 type of ART procedure (e.g. IVF or ICSI or combination), and other treatment information  
170 including controlled ovarian stimulation protocol and ovulation trigger.

171

172 *Classification of study groups*

173 *Route of administration:* The relative benefit of the different routes of progestogen  
174 administration was compared. The most commonly employed routes were intramuscular  
175 (IM) injection and vaginal pessary. However, other reported routes included oral, rectal  
176 and subcutaneous (SC) injection. There were several articles where no luteal support (N=8  
177 study groups) was administered and this control group was used as the reference in the  
178 initial analyses; in the later analyses, the vaginal route of administration was used as the  
179 comparator. The dose of progestogen was not analysed since it was intrinsically linked to  
180 route and further sub-divisions created groups with too few women.

181 *Time to commence supplementation:* A key component of the meta-analysis was to  
182 investigate the effect of the time at which progestogen supplementation commenced. The  
183 start time of each treatment was classified into one of five groups; (1) before oocyte  
184 retrieval; (2) on the day of oocyte retrieval (at oocyte retrieval or evening of); (3) between  
185 oocyte retrieval and embryo transfer; (4) on the day of embryo transfer (ET); (5) after  
186 embryo transfer. In this analysis, the comparator was the control group which received no  
187 luteal support.

188 In a subsequent analysis, study groups were further categorised as progestogen  
189 supplementation that commenced (1) at oocyte retrieval (the day and evening of), or on  
190 (2) the first, (3) second and (4) third day after oocyte retrieval. Most articles detailed this  
191 information directly, however in several articles this was determined utilising other  
192 information such as the oocyte retrieval to embryo transfer time. If there was insufficient  
193 information to state the exact day, then this study group was excluded from this analysis.

194 *Estrogen treatment:* For this analysis, only articles which included a direct estrogen  
195 treatment comparison were included. All study groups which received estrogen as part of  
196 the luteal phase support were coded as treated, while the others were incorporated as the  
197 control comparator. The route of estrogen treatment (oral, transdermal patch or vaginal)  
198 and its timing (around oocyte retrieval or around embryo transfer) was not considered.

199 *Duration of progestogen supplementation:* The study groups were classified based on  
200 whether progestogen supplementation treatment was 3 weeks or less, or greater than 3  
201 weeks. The cut-off at 3 weeks was selected as the approximate time of HCG pregnancy  
202 diagnosis and there was a natural stratification in the studies at 3 weeks of treatment.

203 *Sample size calculation*

204 The sample size for a binomial test (two-sided) was calculated with the overall mean  
205 clinical pregnancy rate of 37% being used as the reference. Thus, at a significance level  
206 of 0.05 with a 90% power of detection, the number of women in each study group required  
207 to detect: 1) an increase of 5 percentage points from the reference rate was 2000, 2) an

208 increase of 10 percentage points was 510 and 3) an increase of 15 percentage points was  
209 229. Alternatively, if all women (n=26,726) were included then a 2 percentage point  
210 change could be detected.

### 211 *Statistical analysis*

212 The statistical approach utilised was binominal logistic regression. The “number of  
213 subjects” was the total number of women who were treated within that study, the “number  
214 of successes” was the number of women with a confirmed clinical pregnancy or live birth  
215 and “the model fitted” was the factor (e.g. route or start time) that was being compared.  
216 The dispersion parameter was set to estimate the residual mean squares of fitted model.  
217 The analysis was performed using GenStat 19<sup>th</sup> Edition (Hemel Hempstead, UK). The data  
218 are presented as odds ratio (OR) with 95% confidence intervals (CI) alongside the number  
219 of study groups (N) and women (n). The use of binomial logistic regression meant that no  
220 estimate of heterogeneity between articles (i.e. estimation of  $I^2$ ) was feasible.

221 *Comparison between different routes of administration:* In the initial analysis, the different  
222 routes of administration (IM, oral, rectal, SC and vaginal) were compared to the control  
223 (no luteal support) group. A further 11 study groups where progestogen was  
224 simultaneously administered by multiple routes (i.e. IM plus vaginal) were excluded from  
225 this analysis. None of the control study groups reported live births, thus the effects of  
226 route of administration on live births were not analysed.

227 *Comparison between the different times at which progestogen supplementation*  
228 *commenced:* The effects of the different start times (before oocyte retrieval, at oocyte  
229 retrieval, between oocyte retrieval and ET, at ET and after ET) on clinical pregnancy rate  
230 were compared to the control group. For the effects on live birth rates, the start times  
231 were compared to commencing supplementation at oocyte retrieval, as no live birth rates  
232 were reported in the control group.

233 *Comparison between different start times when progestogen was given via either*  
234 *intramuscular or vaginal routes:* The two most commonly employed routes (IM and  
235 vaginal) were further analysed to determine if the time at which supplementation  
236 commenced affected pregnancy rates. The comparator group was the “at oocyte retrieval”  
237 group as this included the most study groups and women. Next, the intramuscular and  
238 vaginal routes of progestogen administration were directly compared with vaginal  
239 administration as the comparator group. The data was stratified into the following time  
240 points: before oocyte retrieval, at oocyte retrieval, between oocyte retrieval and ET, at ET  
241 and all times combined (overall).

242 An additional comparison was performed between the intramuscular and vaginal routes of  
243 administration with the data stratified by publication date as follows: 1990-1999, 2000-

244 2009 and 2010-2017. There were no studies reporting the use of vaginal progestogen  
245 supplementation prior to 1990.

246 *Determination of the optimal day after oocyte retrieval to start progestogen*  
247 *supplementation:* The database was further interrogated to compare different specific start  
248 times of progestogen supplementation, with the day of oocyte retrieval acting as the  
249 reference. The times categorised were the first, second and third day after oocyte retrieval.

250 *Effect of co-administration of estrogen with progestogen supplementation:* The data was  
251 analysed in two separate ways (1) with the data categorised by vaginal, IM or all routes  
252 of administration and (2) with data categorised into "at oocyte retrieval" and "between  
253 oocyte retrieval and embryo transfer". In all cases, the comparator was the no estrogen  
254 treatment group.

255 *Effect of duration of progestogen supplementation:* For this, progestogen supplementation  
256 for 3 weeks and less (the comparator) was compared with more than 3 weeks. Initially,  
257 all routes of administration were included, but this was then stratified according to either  
258 intramuscular or vaginal route of administration.

## 259 **Results**

### 260 *Characteristics of identified studies*

261 A total of 82 articles (Supplementary Table 1) including 26,726 women met the selection  
262 criteria, which were published between 1983 and 2018. This created 185 different study  
263 groups/treatments. Both prospective and retrospective studies were incorporated into this  
264 analysis. The prospective studies included "randomised control trials" however a large  
265 proportion of these studies did not have a control-untreated group. More often they were  
266 randomised trials in which two or more different treatments were compared. In respect to  
267 live births, there were fewer study groups (N=65) with a lower number of women  
268 (n=12,006). Consequently, live birth rates were considered as a secondary outcome  
269 measure.

270 The studies were conducted across the World with the greatest proportion of the studies  
271 originating from continental Europe (32%), North America (23%), and the Middle East  
272 (27%). A relatively low percentage of the studies were performed in Asia (13%), the UK  
273 (2%), South America (1%) and Africa (2%).

274 The youngest reported individual in the dataset was 18 years old, while the oldest was 47.  
275 In the majority of articles, the age groups were matched across the different treatments  
276 and the overall mean age was 32.8 years old. The fertilisation rates and number of  
277 embryos transferred (mean: 3.5) were generally stated but not in all studies. The ovarian  
278 stimulation protocol was described in most study groups, with 132 using long GnRH agonist



279 protocols, 10 using a short GnRH agonist flare protocol and 16 with short GnRH antagonist  
280 protocol. However, the induction protocol was not clearly stated in the other study groups  
281 (N=27). A variety of ovarian induction hormones were used within these protocols  
282 including FSH (N=74), HMG (N=19) and both recombinant FSH and HMG (N=42), while  
283 50 study groups did not mention which type of gonadotrophin was used. The most common  
284 treatment used to trigger final oocyte maturation was HCG (N=173), and in the remaining  
285 12 study groups the ovulation trigger was not detailed.

286 The aetiology of the specific infertility was mentioned in only 5 study groups, where women  
287 were at risk of ovarian hyper-stimulation syndrome (OHSS). Thus, there was insufficient  
288 information to dissect the benefits of progestogen supplementation according to different  
289 underlying pathologies to warrant further investigation.

#### 290 *Risk of bias*

291 Most articles (including those reporting control study groups) were identified as having an  
292 unclear or high risk of bias in one or more domain (Supplementary Fig 2 & 3), often  
293 resulting from a lack of detail reported in the original methods (e.g. if or how  
294 randomisation was generated). Blinding was considered difficult to achieve given the  
295 markedly different routes of administration (vaginal vs intramuscular) but was thought  
296 unlikely to have introduced significant bias, given the objective nature of pregnancy  
297 outcomes and is not expected to have influenced the outcomes.

298 The potential risk of bias in those articles which included control study groups appeared  
299 broadly similar to that observed across all articles (Supplementary Fig 3). Amongst the  
300 articles reporting control study groups, one (17) was judged to have a high risk of selection  
301 bias relating to one of the treatment groups.

#### 302 *Does progestogen supplementation improve clinical pregnancy rates in women undergoing 303 fresh IVF cycles?*

304 There was a significant benefit to clinical pregnancy rates of either intramuscular (OR=4.57  
305 [CI: 2.19-9.53];  $p<0.001$ ), vaginal (OR=3.34 [CI: 1.61-6.91];  $p<0.01$ ), subcutaneous  
306 (OR=3.36 [CI: 1.44-7.83];  $p<0.01$ ) or oral (OR=2.57 [CI: 1.19-5.58];  $p<0.05$ )  
307 progestogen supplementation (Fig 1A) versus no treatment. Numerically, this was  
308 equivalent to increasing mean pregnancy rates from 14.7% for untreated women to 30.7%  
309 following oral, 36.4% following vaginal, 36.6% following subcutaneous, and 44.0%  
310 following intramuscular progestogen supplementation. While rectal (OR=2.32 [CI: 0.62-  
311 8.68];  $p>0.05$ ) routes of administration offered no benefit, although this route was poorly  
312 represented.

313 *When is the optimal time to start progestogen supplementation?*

314 The relative benefit to clinical pregnancy rates of commencing progestogen  
315 supplementation at different times was compared with no supplementation (Fig 1B). There  
316 was a clear benefit of progestogen supplementation at oocyte retrieval, at embryo transfer  
317 or between these events as well as after embryo transfer. The greatest benefit was clearly  
318 observed when progestogen administration commenced between oocyte retrieval and  
319 embryo transfer (OR=4.76 [CI: 2.35-9.67];  $p < 0.001$ ). Furthermore, when at oocyte  
320 retrieval and between oocyte retrieval and embryo transfer were directly compared then  
321 there was a clear benefit of starting progesterone administration between oocyte retrieval  
322 and embryo transfer (OR=1.31 [CI: 1.10-1.58],  $p < 0.01$ ). In contrast, there was no benefit  
323 to clinical pregnancy rates versus untreated women when progestogen treatment  
324 commenced before oocyte retrieval (OR=2.10 [CI: 0.95-4.66];  $p > 0.05$ ).

325 *Does the optimal time to commence progestogen supplementation vary by route of*  
326 *administration?*

327 In order to address this, the control untreated group was excluded and the different start  
328 times were compared to starting progestogen supplementation at oocyte retrieval. There  
329 were insufficient study groups and women to include the after ET group. Additionally,  
330 intramuscular and vaginal routes of administration were analysed separately.

331 When progestogen was administered intramuscularly, starting progestogen  
332 supplementation before oocyte retrieval (OR=0.32 [CI: 0.16-0.63];  $p < 0.01$ ) was less  
333 favourable to clinical pregnancy rates than administration commencing at oocyte retrieval  
334 (Fig 2A). There was no statistically significant benefit to clinical pregnancy rates of  
335 commencing progestogen supplementation between oocyte retrieval and embryo transfer  
336 (OR=1.30 [CI: 0.97-1.75];  $p = 0.08$ ) or at embryo transfer (OR=0.75 [CI: 0.44-1.28];  
337  $p > 0.05$ ).

338 When progestogen was administered vaginally, the greatest benefit to clinical pregnancy  
339 rates was observed when administration began between oocyte retrieval and embryo  
340 transfer (OR=1.38 [CI: 1.10-1.74];  $p < 0.01$ ). While not significant ( $p > 0.05$ ), the odds  
341 ratio for clinical pregnancy rate was numerically lower when starting supplementation  
342 before oocyte retrieval (OR=0.77 [CI: 0.46-1.28]) or at embryo transfer (OR=0.85 [CI:  
343 0.68-1.07] when compared with at oocyte retrieval (Fig 2B).

344 Thus, it appeared that commencing progestogen supplementation before oocyte retrieval  
345 vaginally was less detrimental to clinical pregnancy rates than following intramuscular  
346 treatment. This indicated that when progestogen was administered intramuscularly or  
347 vaginally, the supplementation start times differentially influenced clinical pregnancy  
348 outcomes.

349 In respect to live birth rates, across all routes combined, there was a clear benefit of  
350 commencing supplementation between oocyte retrieval and embryo transfer (OR=1.33  
351 [CI: 1.04-1.69],  $p < 0.05$ ) when compared with at oocyte retrieval (Fig 2C). In contrast,  
352 live birth rates were decreased when progestogen supplementation commenced before  
353 oocyte retrieval (OR=0.52 [CI: 0.30-0.92],  $p < 0.05$ ). However, live birth rates were no  
354 different when progestogen was supplemented at embryo transfer (OR=0.84 [CI: 0.65-  
355 1.08];  $p > 0.05$ ).

356 *Which route of progestogen administration (IM or vaginal) is more beneficial in terms of*  
357 *clinical pregnancy and live birth rates?*

358 When all time-points were combined for each route, intramuscular progestogen  
359 administration offered the greatest overall benefit to clinical pregnancy rates (OR=1.37  
360 [CI: 1.15-1.63],  $p < 0.001$ ) versus vaginal administration. Furthermore, intramuscular  
361 progestogen supplementation was more beneficial to clinical pregnancy rates than the  
362 vaginal route at oocyte retrieval (OR=1.42 [CI: 1.14-1.76];  $p < 0.01$ ). Similar patterns  
363 were observed between oocyte retrieval and embryo transfer (OR=1.33 [CI: 0.96-1.85])  
364 and at embryo transfer (OR=1.24 [CI: 0.68-2.27]) but these failed to reach significance  
365 ( $p > 0.05$ ; Fig 3A). Conversely, when progestogen supplementation commenced before  
366 oocyte retrieval (data not shown), vaginal progestogen administration showed numerically  
367 greater clinical pregnancy rates (OR = 0.59 [CI: 0.427-1.32] but this was not significant  
368 ( $p > 0.05$ ), largely due to a small number of study groups (N=4) in each treatment for this  
369 timeframe.

370 Over time, the proportion of women enrolled in studies administering progestogens  
371 intramuscularly (versus vaginal) has decreased (Supplementary Table 2). However, in  
372 both the 2000-2009 and 2010-2017 timeframes intramuscular progestogen administration  
373 offered a greater benefit to clinical pregnancy rates versus vaginal treatment ( $p < 0.05$ ).  
374 The data was also analysed to confirm whether intramuscular progestogen  
375 supplementation was also of benefit to live birth rates. Fewer studies reported live birth  
376 rates (in total 10391 women), with intramuscular (N=27, n=2910) and vaginal (N=31,  
377 n=7481) progestogen supplementation having equivalent live birth rates (OR=1.17 [CI:  
378 0.89-1.53];  $p > 0.05$ ).

379 *What is the optimal day after oocyte retrieval to start progestogen supplementation?*

380 The previous analysis demonstrated that progestogen supplementation was most  
381 beneficial when it commenced between oocyte retrieval and embryo transfer. Thus, further  
382 analysis was performed to determine the exact optimal day within this window. This  
383 included 149 study groups and supplementation by intramuscular, vaginal, oral and  
384 subcutaneous routes. The day of oocyte retrieval was used as the comparator (Fig 3B).

385 Commencing progestogen supplementation on the day after oocyte retrieval was most  
386 beneficial in terms of clinical pregnancy rates (OR=1.25 [CI: 1.02-1.54];  $p < 0.05$ ). Starting  
387 supplementation on the second day after oocyte retrieval had equivalent clinical pregnancy  
388 rates to at oocyte retrieval (OR=1.10 [CI: 0.88-1.36];  $p > 0.05$ ). In contrast, further  
389 delaying supplementation until the third day (OR=0.66 [CI: 0.50-0.87];  $p < 0.01$ ) reduced  
390 clinical pregnancy rates versus starting at oocyte retrieval (Fig 3B). No significant  
391 differences in live birth rates were detected between the different start days ( $p > 0.05$ ; data  
392 not shown).

393 *Does the addition of estrogen treatment to progestogen supplementation improve clinical*  
394 *pregnancy rates?*

395 The co-administration of estrogen was of no overall benefit to clinical pregnancy rates  
396 (OR=1.33 [CI: 0.90-1.97;  $p > 0.05$ ]). Furthermore, this lack of benefit was observed when  
397 progestogens were co-administered by either the vaginal (OR=1.40 [CI: 0.84-2.34;  
398  $p > 0.05$ ) or intramuscular route (OR=1.04 [CI: 0.50-2.14;  $p > 0.05$ ]) (Fig 4A). Clinical  
399 pregnancy rates were similar following the addition of estrogen to progestogen  
400 supplementation that commenced at oocyte retrieval (OR=1.29 [CI: 0.72-2.34];  $p > 0.05$ )  
401 and between oocyte retrieval and embryo transfer (OR=1.59 [CI: 0.85-2.95];  $p > 0.05$ )  
402 (Fig 4B). Similarly, live birth rates were not improved by the addition of estrogen  
403 supplementation ( $p > 0.05$ ; data not shown).

404 *Does the duration of progestogen supplementation effect clinical pregnancy and live birth*  
405 *rates?*

406 Overall, there was no difference in clinical pregnancy rate when progestogen  
407 supplementation was continued for up to 12 weeks (OR=1.06 [CI: 0.87-1.29];  $N=115$ ,  
408  $n=17,215$ ;  $p > 0.05$ ) compared with ceasing after 3 weeks ( $N=41$ ,  $n=5357$ ). Similarly, if  
409 the duration of progestogen supplementation was categorised into smaller 2 or 3 weekly  
410 intervals, then there was no particular timeframe that was of greater benefit than ceasing  
411 supplementation after three weeks (data not shown). When the data was subdivided based  
412 on route of progestogen supplementation (intramuscular or vaginal) then extending  
413 progestogen supplementation was not beneficial to clinical pregnancy rates when it was  
414 administered intramuscularly (OR=1.23 [CI: 0.85-1.78];  $N=17$ ,  $n=1486$  [ $\leq 3$  weeks] vs  
415  $N=29$ ,  $n=3771$  [3-12 weeks];  $p > 0.05$ ) or vaginally (OR= 0.94 [CI: 0.75-1.19];  $N=15$ ,  
416  $n=3338$  [ $\leq 3$  weeks] vs  $N=72$ ,  $n=10654$  [3-12 weeks];  $p > 0.05$ ).

417 The dataset was more limited when considering live births. Overall, continuing  
418 progestogen supplementation for  $> 3$  weeks similarly had no benefit to live birth rates  
419 (OR=1.11 [CI: 0.88-1.46];  $N=17$ ,  $n=3411$  [ $\leq 3$  weeks] vs  $N=46$ ,  $n=8121$  [3-12 weeks];  
420  $p > 0.05$ ). When the data was subdivided based on whether progestogen supplementation

421 was via intramuscular or vaginal routes then extending progestogen supplementation had  
422 no benefit when administered vaginally (OR=1.31 [CI: 0.99-1.74]; N=6, n=2431 [ $\leq$ 3  
423 weeks] vs N=24, n=4878 [3-12 weeks]; p=0.06) or when administered intramuscularly  
424 (OR= 0.72 [CI: 0.43-1.20]; N=10, n=960 [ $\leq$ 3 weeks] vs N=16, n=1648 [3-12 weeks];  
425 p>0.05).

426

## 427 **Discussion**

428 Progestogen supplementation was of benefit to clinical pregnancy rates when administered  
429 intramuscularly, subcutaneously, orally or vaginally. The best response was observed  
430 when administration commenced at or following oocyte retrieval. The benefit was less  
431 however, if progestogen supplementation was delayed for 2 or more days after oocyte  
432 retrieval, likely reflecting the benefit of exogenous progestogen prior to embryo transfer.  
433 The most commonly reported routes of progestogen supplementation were intramuscular  
434 and vaginal. Both routes improved clinical pregnancy rate versus no treatment, with most  
435 benefit observed following intramuscular administration.

436 Progestogen supplementation was found to be of some benefit to clinical pregnancy rates,  
437 ongoing pregnancy and live birth versus placebo or no-treatment in a Cochrane review of  
438 875 women across 8 randomised controlled trials (10). Also in that review intramuscular  
439 progestogen was of more benefit than vaginal/rectal (OR=1.24, [CI: 1.03-1.50]) in  
440 respect to live birth rates. However, a difference between these two routes was not  
441 detected when clinical pregnancy rates were considered (13 RCTs, 2932 women). The  
442 present study utilised a distinctive and robust statistical approach, enabling a broad-  
443 ranging scope which incorporates retrospective studies. Importantly, it revealed that  
444 intramuscular progestogen was of greater benefit to clinical pregnancy rates than vaginal  
445 progestogen (153 study groups, 22852 women). This was particularly evident when  
446 administration commenced at oocyte retrieval.

447 Intramuscular administration offered most benefit to clinical pregnancy rate in the current  
448 study, however, it represented only 26% of treatments, with the majority (62%) of  
449 supported cycles using vaginal administration. In a survey of luteal phase support in 408  
450 treatment centres from 82 countries, vaginal progestogens were administered alone in  
451 77% of supplemented cycles (9). Furthermore, the clinical use of intramuscular  
452 progestogens for the support of assisted reproduction has declined in recent years from  
453 13% to around 5%, although it has traditionally been the most popular form of luteal  
454 support in the United States (9, 15).

455 Vaginal progestogen preparations may be preferred by patients to intramuscular  
456 preparations (18, 19). Vaginal treatments are reportedly well tolerated, due to their ease

457 and relative convenience, whilst patients find the injections painful and report high rates  
458 of irritation at the intramuscular injection site (18). In addition, rare but significant side  
459 effects have been reported following intramuscular luteal support (20-23). Vaginal  
460 progestogens are not free from disadvantages however; they may require multiple daily  
461 applications, can lead to vaginal irritation or discharge in some women (24) and the  
462 preparations may leak which is unpleasant and leads to variable exposure.

463 The routes of progestogen administration exhibit different pharmacological profiles. Oral  
464 progesterone has very poor bioavailability, does not produce a sustained plasma  
465 progesterone concentration (25), fails to elicit an adequate endometrial secretory response  
466 (26) and produces sedative metabolites (27). In addition, a negative impact on  
467 implantation was observed following oral micronized progesterone versus intramuscular  
468 or vaginal progesterone (28, 29). Administration of the orally effective dydrogesterone led  
469 to clinical pregnancy rates similar to those following intravaginal micronized progesterone  
470 support (30, 31). Recent evidence also suggests that oral dydrogesterone is well tolerated  
471 and is not associated with significant fetal or maternal safety risk (32). Despite this, oral  
472 progesterone has very low current clinical use (9).

473 Intramuscular administration of progesterone results in higher more sustained serum  
474 levels than vaginal administration, however vaginal regimens undergo rapid absorption to  
475 achieve higher endometrial tissue concentrations (33). This preferential uptake of  
476 progesterone has been described as the "first uterine pass effect", with direct local  
477 transport of progesterone from vagina to uterus thought to explain the enhanced uterine  
478 concentrations (34). It has been suggested however, that these raised local progesterone  
479 concentrations may not provide optimal support for ongoing pregnancy (35). Indeed, in  
480 the interim analysis of a recent large-scale randomised control trial evaluating  
481 progesterone replacement in frozen transfer cycles, vaginal progesterone administration  
482 resulted in significantly reduced ongoing pregnancy rates versus intramuscular  
483 supplementation (35), thought to result from early pregnancy loss. Intramuscular  
484 progesterone has been suggested to better support early pregnancy via greater uterine  
485 quiescence (36) and different progestogen formulations may also result in varied  
486 luteotrophic metabolites (37).

487 In a sub-analysis, it was observed that categorising progestogen dosage into low vs high  
488 within intramuscular or vaginal routes revealed that clinical pregnancy rates were not  
489 affected by dosage in either route (data not shown). This is in agreement with the  
490 Cochrane review (10) which demonstrated no effect of dose on live birth rates when  
491 progestogen was administered vaginally.

492 The time at which progestogen treatment began had an impact on its degree of benefit.  
493 This aspect of luteal phase support has received less attention and was not reported on  
494 by van der Linden et al (10). The present study has clearly demonstrated that commencing  
495 luteal support following oocyte retrieval but before embryo transfer provided most benefit  
496 to clinical pregnancy rates, irrespective of route. However, the timing of administration  
497 appeared to be more critical for intramuscular progestogen, where the difference in  
498 response before oocyte retrieval (OR=0.32) was markedly lower than in the window  
499 between oocyte retrieval and embryo transfer (OR=1.30). Similarly, live birth rates were  
500 improved when progestogen supplementation commenced between oocyte retrieval and  
501 embryo transfer compared with commencing at oocyte retrieval. Previous studies (14)  
502 have similarly suggested an ideal window for the initiation of luteal support, between the  
503 evening of oocyte retrieval and day 3, based on a small number of randomised controlled  
504 trials. Others have also suggested that the initiation of intravaginal progestogen is critical  
505 (19), with unfavourable results associated with the early initiation of intravaginal gel.  
506 Furthermore, it has been suggested that the greater bioavailability of vaginal progestogen  
507 to the endometrium may result in precocious development of the endometrial receptivity  
508 window (19).

509 In the current study the benefit observed within the window from oocyte retrieval and  
510 embryo transfer, largely resulted from luteal support that began on the first day after  
511 oocyte retrieval (OR=1.25 vs at oocyte retrieval). This delay in the initiation of luteal  
512 support does not reflect current clinical practice, where in a survey of IVF units, 80.1% of  
513 luteal phase support began on the day of oocyte retrieval, whilst in 15.4% of cycles  
514 progestogen began on the day of embryo transfer (9).

515 The co-administration of estrogen plus progestogen was of no overall benefit to clinical  
516 pregnancy rates (OR=1.33;  $p>0.05$ ). When routes of progestogen supplementation were  
517 considered separately, clinical pregnancy rates did not benefit from the addition of  
518 estrogen to progestogen co-administered by either the vaginal or intramuscular routes.  
519 Equally, there was no benefit to clinical pregnancy rates of estrogen treatment when  
520 different times of progestogen supplementation were considered.

521 Progesterone supplementation is considered obligatory following the luteal deficiency  
522 observed in ART. However, whether supplemental estrogen is also required to ameliorate  
523 the effects of declining luteal estradiol remains a matter of debate. Experimental results  
524 in human and non-human primates have suggested that normal endometrial function  
525 requires only low levels of estradiol (38). Despite this, elevated serum and endometrial  
526 estradiol levels following vaginal administration have been suggested to enhance  
527 endometrial thickness and implantation (39), whilst others report that it may be  
528 detrimental to endometrial receptivity (40). Other studies have failed to find a link between

529 declining estradiol in early or mid-luteal phase of ART cycles and clinical pregnancy or  
530 miscarriage (41).

531 No differences in endometrial histology were observed in women following GnRH  
532 downregulation and progesterone replacement, with or without varying doses of estrogen  
533 (42). In contrast, estrogen receptor antagonist treatment delayed endometrial maturation,  
534 suggesting a requirement for luteal phase estradiol (43). In addition, endometrial gene  
535 expression is altered by controlled ovarian stimulation (44, 45) and proteins were  
536 differentially expressed by human endometrial cells in response to high estradiol (46).

537 There are conflicting clinical reports regarding the value of adding estrogen to luteal  
538 support regimes. Progestogens plus estrogen have been associated with higher clinical  
539 pregnancy rates than progestogens alone (47), although this has varied by route of  
540 administration (48). In contrast other studies have shown no beneficial effect of adding  
541 estrogen (10, 49, 50); indeed adverse effects, such as increased miscarriage, have also  
542 been reported (51). Equally, it is possible that circulating E2 levels following ovarian  
543 stimulation might influence whether further boosting estrogen levels is of benefit (52, 53),  
544 however, analysis of this was not possible due to the lack of reporting of E2 levels.

545 An important consideration in meta-analysis is the consistency between articles, such as  
546 the quantity  $I^2$  (54). In the current study, estimation of  $I^2$  was not feasible as within each  
547 statistical comparison there were relatively few articles in which both treatments were  
548 performed. Thus, reporting  $I^2$  or Cochran's Q statistic would be invalid and not  
549 representative of the data presented.

550 Equally, it is clear from other similar meta-analyses, using different statistical approaches,  
551 that there is often moderate to considerable heterogeneity between studies for a particular  
552 comparison. For example, in the Cochrane review by van der Linden et al (10)  $I^2$  was  
553 estimated to be 71% when comparing intramuscular versus vaginal routes and 56% when  
554 comparing the effect of estrogen supplementation. Potential causes of this heterogeneity  
555 include variations in ovarian stimulation and / or treatment protocols employed and the  
556 characteristics of the patient populations within the different articles.

557 A limitation of the present study was that the number of articles reporting live birth data  
558 was markedly lower than those reporting clinical pregnancy rates. Consequently, the  
559 potential for valid sub-analyses in relation to live birth is more restricted. Another  
560 important consideration is that the different estrogen regimes (start time and route) were  
561 not analysed separately, due to the low number of study groups within each comparison.  
562 It is feasible that the different routes and start time could influence pregnancy outcome  
563 and this warrants further investigation.

564



565 In a worldwide survey of IVF centres, the majority of luteal phase support was continued  
566 up to 8-10 weeks of gestation (44%) or beyond (28%), despite suggestions that it can be  
567 safely discontinued following a positive HCG test (55, 56) or fetal heart pulsations (57).  
568 The rationale for prolonged progesterone is unclear, given that the luteo-placental shift  
569 causes placental progesterone to dominate from the 8<sup>th</sup> week of pregnancy (58). The  
570 presence of significant luteotrophic HCG levels by week 5 of pregnancy also lead others to  
571 support suspending progesterone early (59). Indeed, in the current study there was no  
572 benefit to clinical pregnancy rates of continuing treatment beyond 3 weeks OR=1.06 [CI:  
573 0.87-1.29];  $p>0.05$ ). Similarly, live birth rates were not improved by prolonged  
574 progesterone (intramuscular;  $>3$  weeks v  $\leq 3$  weeks; OR= 1.11).

575

## 576 **Conclusion**

577 Our results have clearly established that progestogen supplementation via the IM route  
578 offers the most benefit to clinical pregnancy. These results demonstrate that the optimal  
579 time to commence supplementation is the day after oocyte retrieval, and that clinical  
580 pregnancy rates were not improved by continued supplementation for greater than 3  
581 weeks or by the additional treatment with estrogens. This lack of improvement occurred  
582 whether the progestogen was administered by the vaginal or intramuscular route.

583 These outcomes are in contrast to current trends in global clinical practice and collectively  
584 suggest that the clinical approach to luteal phase support may not be delivering optimal  
585 benefits. Therefore this study enables the evidence-based re-evaluation of clinical  
586 protocols for progestogen supplementation, the provision of improved informed choice for  
587 patients and ultimately greater pregnancy success for women undergoing fresh IVF cycles.

588

589

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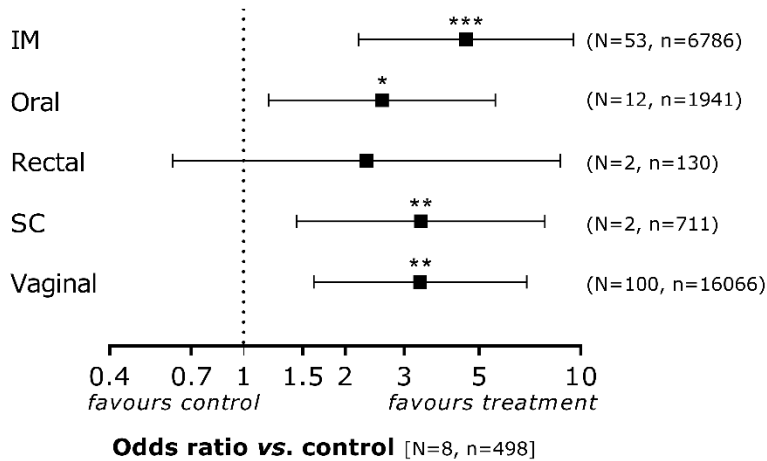
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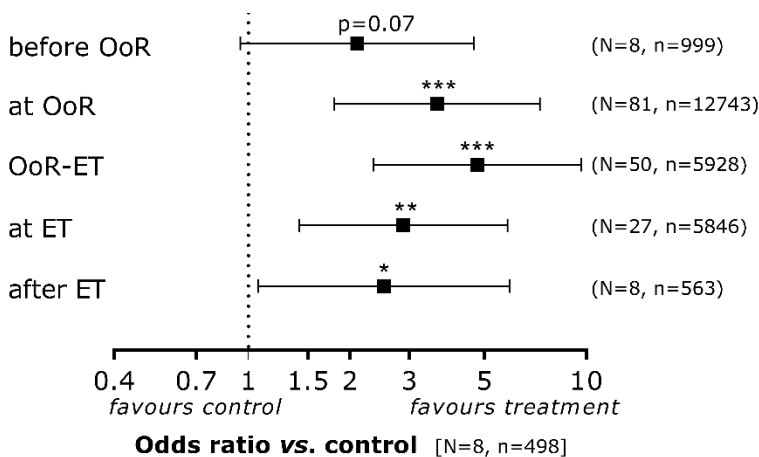
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**A. route**

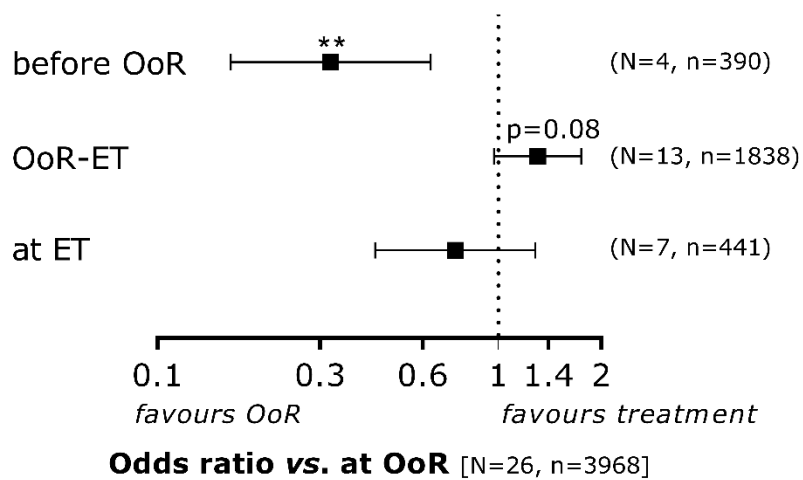


**B. start**

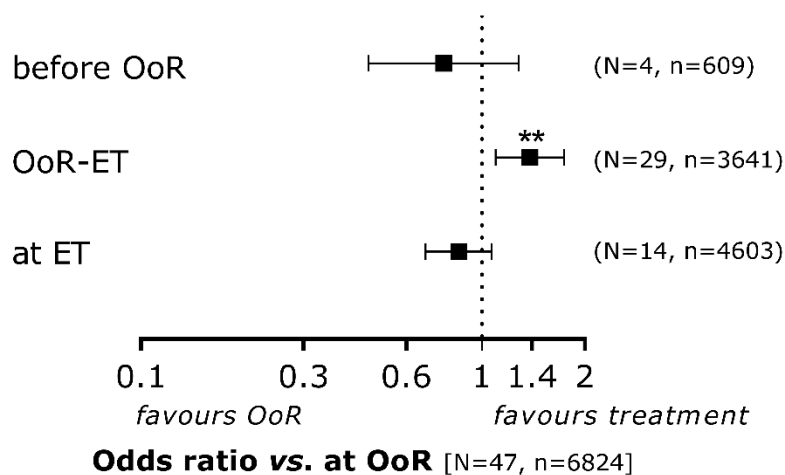


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 772 **Figure 1:** The odds ratio ( $\pm$  95% confidence intervals) for the relative benefit to clinical  
 773 pregnancy of the (A) different routes and (B) start time of progestogen supplementation  
 774 versus no progestogen treatment in women undergoing fresh IVF cycles. In (A),  
 775 progestogens were administered by intramuscular (IM), oral, rectal, subcutaneous (SC) or  
 776 vaginal routes. In (B), the different start times for progestogen supplementation were;  
 777 before the day of oocyte retrieval (before OoR); at oocyte retrieval (at OoR); between  
 778 oocyte retrieval and the day of embryo transfer (OoR-ET); on the day of embryo transfer  
 779 (at ET); after the day of embryo transfer (after ET). The dotted line represents the  
 780 comparative odds ratio for the control (untreated) group. Significant differences between  
 781 treatment and control are indicated as follows: \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ . N  
 782 = number of study groups, n = total number of women, for each treatment or comparator.

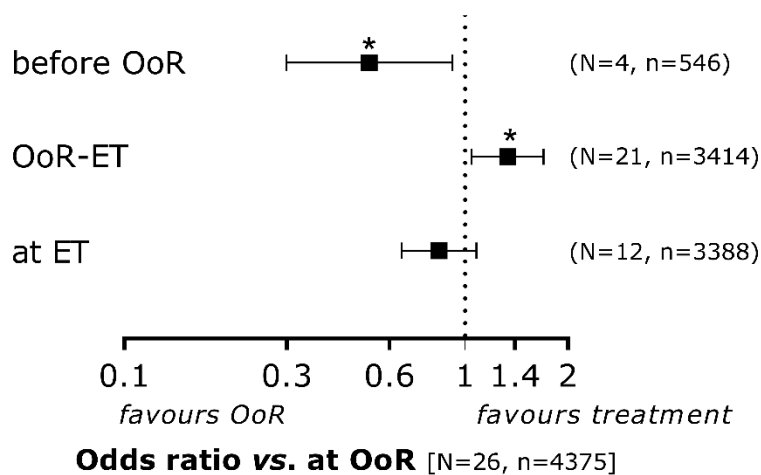
### A. intramuscular (clinical pregnancy)



### B. vaginal (clinical pregnancy)



### C. all routes (live birth)

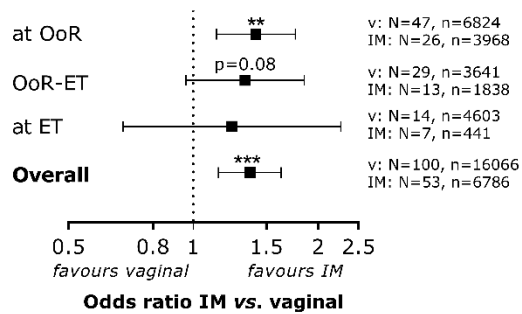


784 **Figure 2:** The odds ratio ( $\pm$  95% confidence intervals) for the relative benefit to clinical  
785 pregnancy of the different times to commence A) intramuscular and B) vaginal  
786 progestogen supplementation, while C) shows the relative benefit to live births of the  
787 different times to commence progestogen supplementation with all routes combined, in  
788 women undergoing fresh IVF cycles. The start times were; before the day of oocyte  
789 retrieval (before OoR); at oocyte retrieval (at OoR); between oocyte retrieval and the day  
790 of embryo transfer (OoR-ET); on the day of embryo transfer (at ET). The dotted line  
791 represents the comparative odds ratio for commencing progestogen at oocyte retrieval  
792 (OoR). Significant differences between treatment and comparator (at OoR) are indicated  
793 as follows: \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ . N = number of study groups, n = total number of  
794 women, for each treatment or comparator.

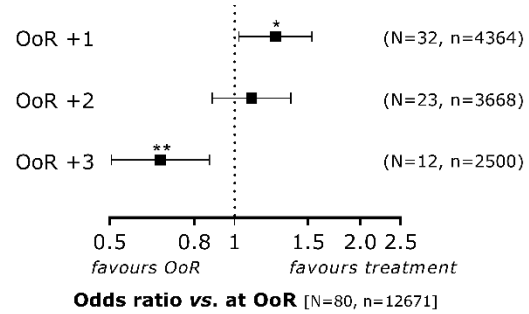
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### A. IM vs. vaginal



### B. start

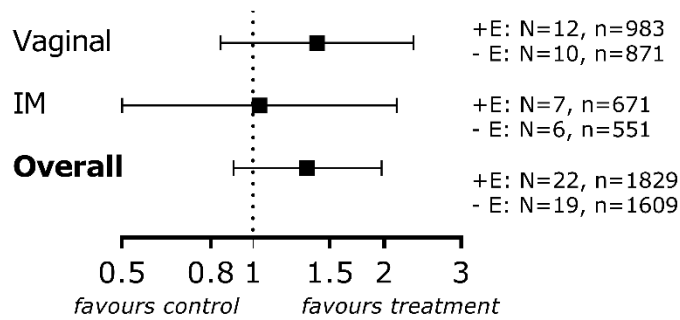


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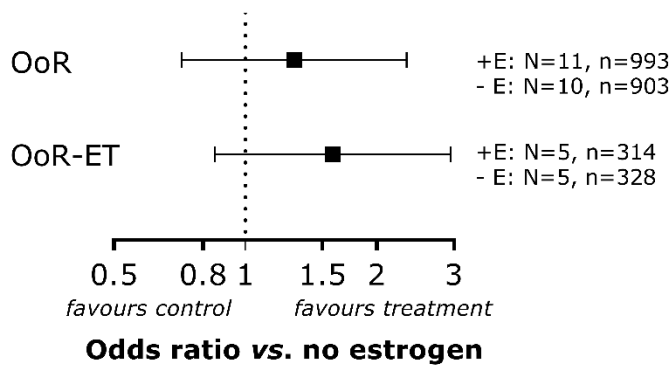
797 **Figure 3:** The odds ratio ( $\pm$  95% confidence intervals) for the relative benefit to clinical  
 798 pregnancy of (A) intramuscular versus vaginal progestogen supplementation and (B)  
 799 commencing on specific days after oocyte retrieval (OoR) in women undergoing fresh IVF  
 800 cycles. In (A), the analysis was split into the different times that treatment began as  
 801 follows: at oocyte retrieval (at OoR); between oocyte retrieval and the day of embryo  
 802 transfer (OoR-ET); on the day of embryo transfer (at ET); at all start times combined  
 803 (Overall). The dotted line represents the comparative odds ratio for vaginal administration  
 804 of progestogen. In (B), all routes of administration were included and the different times  
 805 were as follows: Oocyte retrieval plus 1 day (OoR +1), plus 2 days (OoR +2) and plus 3  
 806 days (OoR +3). The dotted line represents the comparative odds ratio for administration  
 807 of progestogen at oocyte retrieval (OoR). Significant differences between treatment and  
 808 comparator are indicated as follows: \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ . N = number  
 809 of study groups, n = total number of women, for each treatment or comparator. IM,  
 810 intramuscular; v, vaginal.

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**A.**



**B.**



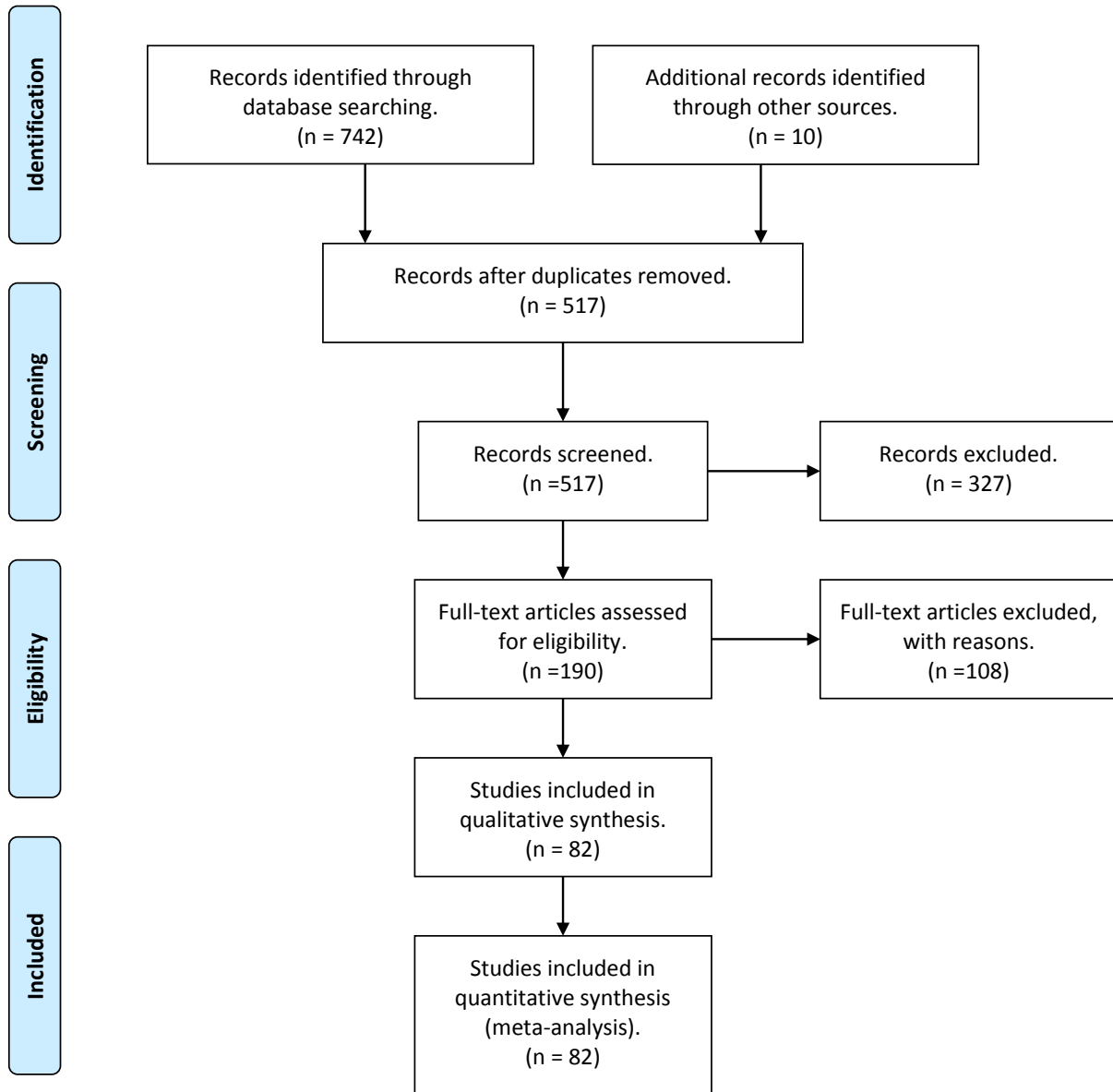
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813 **Figure 4:** The odds ratio ( $\pm$  95% confidence intervals) for the relative benefit to clinical  
814 pregnancy of combining estrogen and progestogen supplementation in women undergoing  
815 fresh IVF cycles. In A), progestogen was administered by vaginal or intramuscular (IM)  
816 routes and all progestogen routes combined (Overall). In B), progestogen administration  
817 commenced at oocyte retrieval (OoR) or between oocyte retrieval and embryo transfer  
818 (OoR-ET). The dotted line represents the comparative odds ratio for progestogen-only  
819 treatment (no estrogen). There were no significant differences between treatment and  
820 comparators. N = number of study groups, n = total number of women, for each treatment  
821 or comparator. +E, plus estrogen; -E, no estrogen.

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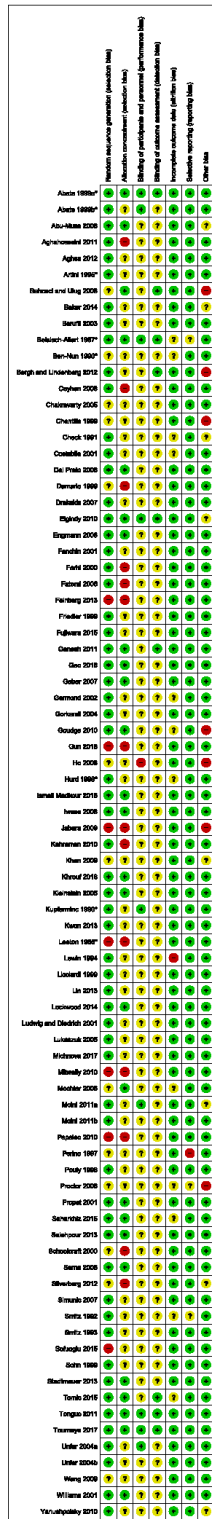
824 **Figure captions – Supplementary**



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826 **Supplementary Figure 1:** PRISMA (Preferred Reporting Items for Systematic Reviews  
827 and Meta-analyses) 2009 flow diagram.

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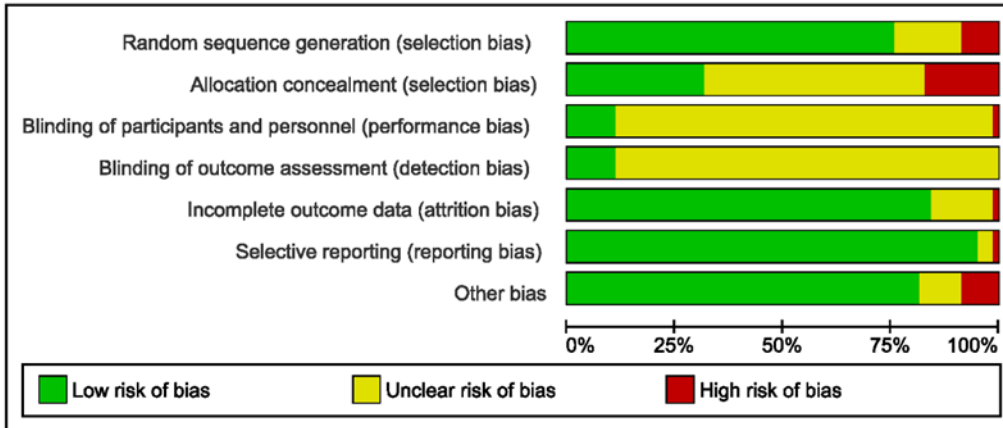


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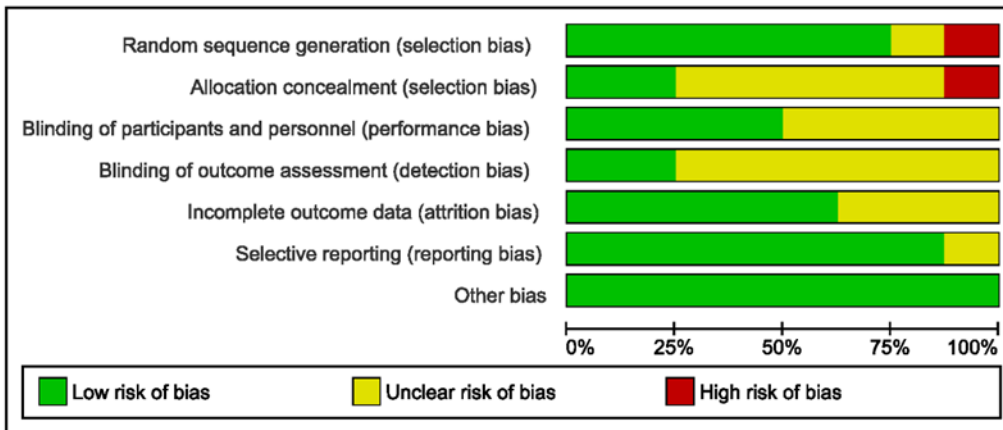
830 **Supplementary Figure 2:** Risk of bias summary: review authors' judgements about  
 831 each risk of bias item for each included study. Articles including control study groups are  
 832 indicated by \*.

833

A



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835 **Supplementary Figure 3:** Risk of bias graphs: review authors' judgements about each  
836 risk of bias item presented as percentages across a) all included studies, and b) those  
837 articles which included control study groups.

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840 **Supplementary Table 1: Summary and bibliography of the studies**  
841 **investigating the effects of progestogen supplementation in**  
842 **women undergoing ART, which met the inclusion criteria and from**  
843 **which data was extracted.**  
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No.	Reference	Year	Region	No. of women	No. of study groups	
845	1	Abate, et al. (1)	1999a	EUROPE	86	2*
846	2	Abate, et al. (2)	1999b	EUROPE	156	3*
847	3	Abu-Musa, et al. (3)	2008	MIDDLE EAST	125	2
848	4	Aghahosseini, et al. (4)	2011	MIDDLE EAST	108	2
849	5	Aghsa, et al. (5)	2012	MIDDLE EAST	147	2
850	6	Artini, et al. (6)	1995	EUROPE	132	3*
851	7	Bahceci and Ulug (7)	2008	MIDDLE EAST	2013	4
852	8	Baker, et al. (8)	2014	USA	782	2
853	9	Baruffi, et al. (9)	2003	S.AMERICA	103	2
854	10	Belaïsch-Allart, et al. (10)	1987	EUROPE	258	2*
855	11	Ben-Nun, et al. (11)	1990	MIDDLE EAST	111	3*
856	12	Bergh and Lindenberg (12)	2012	EUROPE	1983	2
857	13	Ceyhan, et al. (13)	2008	MIDDLE EAST	44	2
858	14	Chakravarty, et al. (14)	2005	ASIA PACIFIC	430	2
859	15	Chantilis, et al. (15)	1999	USA	206	2
860	16	Check, et al. (16)	1991	USA	127	2
861	17	Costabile, et al. (17)	2001	EUROPE	300	2
862	18	Dal Prato, et al. (18)	2008	EUROPE	412	3
863	19	Damario, et al. (19)	1999	USA	271	2
864	20	Drakakis, et al. (20)	2007	EUROPE	77	2
865	21	Elgindy, et al. (21)	2010	MIDDLE EAST	270	3
866	22	Engmann, et al. (22)	2008	UK	166	2
867	23	Fanchin, et al. (23)	2001	EUROPE	84	2
868	24	Farhi, et al. (24)	2000	MIDDLE EAST	285	4
869	25	Fatemi, et al. (25)	2006	EUROPE	182	2
870	26	Feinberg, et al. (26)	2013	USA	681	2
871	27	Friedler, et al. (27)	1999	MIDDLE EAST	64	2
872	28	Fujiwara (28)	2015	ASIA PACIFIC	90	2
873	29	Ganesh, et al. (29)	2011	ASIA PACIFIC	1363	3
874	30	Gao, et al. (30)	2018	ASIA PACIFIC	197	2
875	31	Geber, et al. (31)	2007	MIDDLE EAST	244	2
876	32	Germond, et al. (32)	2002	EUROPE	114	2
877	33	Gorkemli, et al. (33)	2004	MIDDLE EAST	288	2
878	34	Goudge, et al. (34)	2010	USA	97	2
879	35	Gun, et al. (35)	2016	MIDDLE EAST	177	2
880	36	Ho, et al. (36)	2008	ASIA PACIFIC	144	2
881	37	Hurd, et al. (37)	1996	USA	79	2*
	38	Ismail Madkour, et al. (38)	2016	USA	220	2
	39	Iwase, et al. (39)	2008	ASIA PACIFIC	40	2
	40	Jabara, et al. (40)	2009	USA	292	2
	41	Kahraman, et al. (41)	2010	MIDDLE EAST	426	2
	42	Khan, et al. (42)	2009	USA	240	4
	43	Khrouf, et al. (43)	2016	AFRICA	186	3
	44	Kleinsteïn (44)	2005	EUROPE	430	2
	45	Kupfermînc, et al. (45)	1990	MIDDLE EAST	105	2*

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No.	Reference	Year	Region	No. of women	No. of study groups
46	<a href="#">Kwon, et al. (46)</a>	2013	ASIA PACIFIC	108	2
47	<a href="#">Leeton, et al. (47)</a>	1985	ASIA PACIFIC	186	3*
48	<a href="#">Lewin, et al. (48)</a>	1994	MIDDLE EAST	100	2
49	<a href="#">Licciardi, et al. (49)</a>	1999	USA	43	2
50	<a href="#">Lin, et al. (50)</a>	2013	ASIA PACIFIC	402	4
51	<a href="#">Lockwood, et al. (51)</a>	2014	UK	640	2
52	<a href="#">Ludwig and Diedrich (52)</a>	2001	EUROPE	126	2
53	<a href="#">Lukaszuk, et al. (53)</a>	2005	EUROPE	224	3
54	<a href="#">Michnova, et al. (54)</a>	2017	EUROPE	100	2
55	<a href="#">Mitwally, et al. (55)</a>	2010	USA	544	2
56	<a href="#">Mochtar, et al. (56)</a>	2006	EUROPE	298	3
57	<a href="#">Moini, et al. (57)</a>	2011a	MIDDLE EAST	98	2
58	<a href="#">Moini, et al. (58)</a>	2011b	MIDDLE EAST	153	3
59	<a href="#">Papaleo, et al. (59)</a>	2010	EUROPE	172	2
60	<a href="#">Perino, et al. (60)</a>	1997	EUROPE	300	2
61	<a href="#">Pouly, et al. (61)</a>	1996	EUROPE	283	2
62	<a href="#">Proctor, et al. (62)</a>	2006	USA	358	2
63	<a href="#">Propst, et al. (63)</a>	2001	USA	201	2
64	<a href="#">Saharkhiz, et al. (64)</a>	2015	MIDDLE EAST	210	2
65	<a href="#">Salehpour, et al. (65)</a>	2013	MIDDLE EAST	80	2
66	<a href="#">Schoolcraft, et al. (66)</a>	2000	USA	89	2
67	<a href="#">Serna, et al. (67)</a>	2008	EUROPE	160	2
68	<a href="#">Silverberg, et al. (68)</a>	2012	USA	474	2
69	<a href="#">Simunic, et al. (69)</a>	2007	EUROPE	266	2
70	<a href="#">Smitz, et al. (70)</a>	1992	EUROPE	262	2
71	<a href="#">Smitz, et al. (71)</a>	1993	EUROPE	378	2
72	<a href="#">Sofuoglu, et al. (72)</a>	2015	MIDDLE EAST	463	2
73	<a href="#">Sohn, et al. (73)</a>	1999	USA	282	2
74	<a href="#">Stadtmauer, et al. (74)</a>	2013	USA	1297	2
75	<a href="#">Tomic, et al. (75)</a>	2015	EUROPE	831	2
76	<a href="#">Tonguc, et al. (76)</a>	2011	MIDDLE EAST	285	3
77	<a href="#">Tournaye, et al. (77)</a>	2017	EUROPE	967	2
78	<a href="#">Unfer, et al. (78)</a>	2004a	EUROPE	734	2
79	<a href="#">Unfer, et al. (79)</a>	2004b	EUROPE	284	2
80	<a href="#">Wang, et al. (80)</a>	2009	ASIA PACIFIC	460	2
81	<a href="#">Williams, et al. (81)</a>	2001	USA	126	2
82	<a href="#">Yanushpolsky, et al. (82)</a>	2010	USA	407	2



907 **Supplementary Table 2:** The relative benefit to clinical pregnancy between  
 908 intramuscular and vaginal progestogen supplementation in women undergoing fresh IVF  
 909 cycles, stratified by decade.

<b>Decade</b>	<b>Number of study groups (N), number of women (n); pregnancy rate</b>	<b>Odds ratio<sup>1</sup> (95% CI)</b>	<b>P-value</b>
1990-1999	N=21, n=2379; 32.3% (vaginal)	<b>1.27</b> (0.94-1.71)	ns
	N=23, n=2277; 36.8% (IM)		
2000-2009	N=58, n=11086; 39.4% (vaginal)	<b>1.38</b> (1.07-1.79)	p<0.05
	N=18, n=3289; 44.3% (IM)		
2010-2017	N=21, n=2601; 33.2% (vaginal)	<b>2.33</b> (1.62-3.35)	p<0.001
	N=10, n=1114; 51.2% (IM)		

910 <sup>1</sup>reference route of administration is vaginal. IM: intramuscular

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