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1 **Management of first-trimester miscarriage: a systematic review and network meta-**
2 **analysis**

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21

22 Running title: Management of first-trimester miscarriage

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24

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46 **Abstract**

47 **Background:** First-trimester miscarriage affects up to a quarter of women worldwide. With
48 many competing treatment options available, there is a need for a comprehensive evidence
49 synthesis.

50 **Objectives and rationale:** We conducted a systematic review and network meta-analysis to
51 assess the effectiveness and safety of treatment options for first-trimester miscarriage:
52 expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration
53 (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO),
54 mifepristone+misoprostol (MIFE+MISO) and misoprostol plus electric vacuum aspiration
55 (MISO+EVAC).

56 **Search methods:** We searched MEDLINE, Embase, CINAHL, AMED and Cochrane
57 Library from inception till June 2018. We included randomised trials of women with first-
58 trimester miscarriage (<14 weeks gestation) and conducted a network meta-analysis
59 generating both direct and mixed evidence on the effectiveness and side effects of available
60 treatment options. The primary outcome was complete evacuation of products of conception.
61 We assessed the risk of bias and the global network inconsistency. We compared the surface
62 under the cumulative ranking curve (SUCRA) for each treatment.

63 **Outcomes:** A total of 46 trials (9250 women) were included. The quality of included studies
64 was overall moderate with some studies demonstrating a high risk of bias. We detected
65 unexplained inconsistency in evidence loops involving MIFE+MISO and adjusted for it. EXP
66 had lower effectiveness compared to other treatment options. The effectiveness of medical
67 treatments was similar compared to surgery. Mixed evidence of low confidence suggests
68 increased effectiveness for MIFE+MISO compared to MISO alone (RR 1.49, 95% CI 1.09-
69 2.03). Side effects were similar among all options. Fewer women needed analgesia following
70 EVAC compared to MISO (RR for MISO 0.43, 95% CI 0.27-0.68) and in the EXP group

71 compared to EVAC (RR 2.07, 95% CI 1.25-3.41). MVA had higher ranking (low likelihood)
72 for post-treatment infection and serious complications (SUCRA 87.6%, 79.2% respectively)
73 with the highest likelihood for post-treatment satisfaction (SUCRA 98%).

74 **Wider implications:** Medical treatments for first-trimester miscarriage have similar
75 effectiveness and side effects compared to surgery. The addition of MIFE could increase the
76 effectiveness of MISO and reduce side effects, although evidence is limited due to
77 inconsistency. EXP has lower effectiveness compared to other treatment options.

78

79 **Systematic review registration:** Prospero CRD42016048920

80

81 **Keywords:** miscarriage, pregnancy loss, first trimester, effectiveness, woman, systematic
82 review, network meta-analysis.

83

84 **Introduction**

85 First trimester miscarriage, the most common time of pregnancy loss, is estimated to affect
86 up to a quarter of pregnant women in their lifetime (Wang *et al.*, 2003). Miscarriage can lead
87 to significant clinical and emotional morbidity, affecting the couples' quality of life (Jurkovic
88 *et al.*, 2013). Providing patient-centred care can help to reduce the psychological sequelae
89 associated with miscarriage (van den Berg *et al.*, 2017) such as increased anxiety, depression,
90 grief and low self-esteem (Frost and Condon, 1996; Swanson *et al.*, 2009). The burden of
91 miscarriage on healthcare resources is significant, leading to over 50,000 hospital admissions
92 annually in the UK (The National Institute for Health and Care Excellence, 2012), with a
93 similar impact in other developed countries (Queensland Clinical Guidelines, 2015; The
94 American College of Obstetricians and Gynecologists, 2015).

95

96 Various treatment options exist for couples experiencing first-trimester miscarriage; these are
97 broadly categorised into expectant, medical and surgical groups (Trinder *et al.*, 2006). The
98 wide use of less invasive treatments such as prostaglandins and manual vacuum evacuation
99 could reduce the need for surgical interventions under general anaesthesia and the number of
100 hospital admissions (Jurkovic *et al.*, 2013; Sotiriadis *et al.*, 2005). Misoprostol is currently
101 the most used drug for treating miscarriage, however, there is no consensus on the best dose
102 and route of its administration (Neilson *et al.*, 2013). Combining medical and surgical
103 treatments is common, though evidence to support this practice is imprecise (Fang *et al.*,
104 2009). Evidence concerning the effectiveness and safety of available treatment options is
105 limited to pairwise comparisons in randomised trials and their meta-analyses (Nanda *et al.*,
106 2006; Neilson *et al.*, 2013; Sotiriadis *et al.*, 2005; Tunçalp *et al.*, 2010).

107

108 There is a need for a comprehensive evidence synthesis to compare the effectiveness and
109 safety of the available treatment options. We conducted a systematic review and a network
110 meta-analysis of randomised trials (comparing different treatments for a particular condition
111 using the estimated effect size from direct and indirect comparisons) (Al Wattar *et al.*, 2017)
112 to assess the effectiveness and side effects of available treatment options for complete
113 evacuation of products of conception in women experiencing first-trimester miscarriage.

114

115 **Methods**

116 We conducted our systematic review according to a prospectively registered protocol
117 (Prospero CRD42016048920) and reported the findings to comply with the extended
118 PRISMA guidelines (Hutton *et al.*, 2015). The final author affirms that the manuscript is an
119 honest, accurate, and transparent account of the study being reported; no important aspects of
120 the study have been omitted; and there are no discrepancies from the planned study protocol.

121

122 ***Search strategy***

123 We searched the following electronic databases for randomised trials comparing any
124 treatment option for first-trimester miscarriage from inception until June 2018 (MEDLINE,
125 Embase, CINAHL, AMED and Cochrane Library). We developed a multi-step search
126 strategy and adjusting it appropriately for each database (not shown). No search filters were
127 applied. We conducted supplementary searches in Google Scholar and Scopus. We manually
128 screened bibliographies of reviewed articles to identify any additional relevant trials. Articles
129 in non-English language were obtained and translated if deemed relevant. We contacted
130 authors for further information when needed, but no unpublished data were included. We
131 reviewed all available systematic reviews on the management of first-trimester miscarriage to
132 identify any additional studies.

133

134 ***Selection criteria and data extraction***

135 We included all randomised trials that evaluated any treatment option in women with first-
136 trimester miscarriage (defined as a spontaneous loss of a non-viable intrauterine pregnancy
137 between 0 and 14 weeks' gestation) (The National Institute for Health and Care Excellence,
138 2012). Studies that included a combination of two treatment options (e.g. medical plus
139 surgical) were included. Studies with multiple comparison arms were also included. We
140 excluded quasi-randomised studies and those reporting on elective termination of pregnancy.
141 Studies that compared variations of the same treatment in both arms (e.g. misoprostol 400 µg
142 vs misoprostol 600 µg) were reported narratively and excluded from the meta-analysis.
143 Studies that reported on secondary outcomes only were also excluded.

144 We manually extracted data, using a bespoke electronic tool, on the place of the study, the
145 publication journal, treatment settings, population characteristics, the treatment options
146 evaluated, including its dose and route where applicable, and primary and secondary
147 outcomes. The selection and data extraction processes were conducted in duplicate by two
148 independent reviewers (BHA and NM). Any disagreement was resolved by discussion with a
149 third reviewer (KSK).

150

151 ***Primary and secondary outcomes***

152 Our primary outcome was complete evacuation of products of conception, defined clinically
153 or on ultrasound as an empty uterine cavity without the need for further treatment. Secondary
154 outcomes were: serious complications (defined as a composite of any of the following:
155 uterine perforation, cervical tear, hysterectomy, laparotomy, Asherman's syndrome, and
156 death), need for blood transfusion, post-treatment infection/pelvic inflammatory disease,
157 nausea, vomiting, diarrhoea, fever (>38 °C with no evidence of infection), patient

158 satisfaction, mean hospital stay (days), visual analogue pain scores, anxiety, depression and
159 need for analgesia.

160

161 *Types of treatment for first trimester miscarriage*

162 Treatment options were grouped into five categories: expectant (defined as conservative
163 management with no active intervention including placebo), medical (defined as any medical
164 drug of any dose, route and format to achieve uterine evacuation), placebo (defined as a
165 planned placebo intervention within a trial settings), surgical (defined as any surgical
166 instruments used under general or local anaesthesia to achieve uterine evacuation) and a
167 combination of any medical plus surgical treatment used consecutively. To reduce
168 inconsistency in the network, we combined conservative and placebo treatments under the
169 same label (expectant management). We also excluded uncommon medical drugs that were
170 reported in single studies (e.g. Methotrexate) and reported on them narratively.

171

172 *Quality assessment of risk of bias*

173 We assessed the risk of bias in all included studies in duplicate by two independent reviewers
174 (BHA and NM) using the Cochrane risk of bias assessment tool (Higgins *et al.*, 2011). This
175 included assessment of the following items: randomisation and sequence generation,
176 allocation concealment, blinding and performance, outcome assessment, completeness of
177 outcome data and selective outcome reporting. Unblinded studies were not penalised in the
178 risk of bias assessment due to the nature of the treatments that makes blinding non-feasible.
179 Quality assessment was performed in duplicate by two independent reviewers.

180

181 *Statistical analysis*

182 We performed standard pairwise meta-analyses using a random-effects model (Sutton *et al.*,
183 2000) and network meta-analysis within a frequentist framework with multivariate meta-
184 analysis models (White *et al.*, 2012), exploiting the direct and indirect randomised evidence
185 to determine the relative effects and ranking. We reported on direct evidence (from head to
186 head comparison of treatments) and mixed evidence (combining both direct and indirect
187 evidence from comparison of treatments) using weighted mean difference (WMD) for
188 continuous outcomes and risk ratios (RR) for dichotomous outcomes with 95% confidence
189 intervals (CI). We also computed the probability that each treatment is the most effective, as
190 well as the surface under the cumulative ranking curve (SUCRA) to compare the relative
191 ranking probability of each treatment (Chaimani *et al.*, 2013; Salanti *et al.*, 2011). Providing
192 a cumulative rankogram adjusts for any uncertainty in the relative treatment effect where
193 limited evidence exists (Chaimani *et al.*, 2013). A cumulative rank provides the probability
194 for each treatment to be the best among the rang of available treatment options; the SUCRA
195 is a transformation of the mean rank accounting for the location and variance of available
196 treatment effects to generate a treatment hierarchy (Salanti *et al.*, 2011).

197 In pairwise meta-analyses, we estimated different heterogeneity variances for each pairwise
198 comparison, using the I^2 index, to capture the percentage of variation that is not due to
199 chance. In the network meta-analysis, we assumed a common estimate for the heterogeneity
200 variance across the different comparisons. To check the assumption of consistency in the
201 entire network, we used the design-by-treatment model (Higgins *et al.*, 2012). In case of
202 whole network inconsistency, we investigated differences between direct and indirect
203 evidence using the loop-specific approach (Bucher *et al.*, 1997), assuming a common
204 heterogeneity estimate within each loop (a loop of evidence exist when numerous trials
205 compare a minimum of three treatments e.g A vs B vs C) (Veroniki *et al.*, 2013). We
206 investigated any detected inconsistency and adjusted for unexplained inconsistency within the

207 network using established models in STATA (Riley *et al.*, 2017). All analyses were done
208 using STATA statistical software, release 14 (StataCorp, College Station, TX,
209 2015).(Chaimani *et al.*, 2013; White, 2011; White *et al.*, 2012).

210

211 ***Patient involvement***

212 We did not involve a patient representative in the design of our study. We consulted the
213 James Lind Library and previous Cochrane reviews to identify the primary outcome and
214 other outcomes of interest to stakeholders.

215

216 **Results**

217 ***Characteristics of included studies***

218 Our electronic search identified 3648 potentially relevant studies. Of these, we excluded 3523
219 after reviewing titles and abstracts. The remaining 125 studies were assessed in full. Eleven
220 studies were identified from screening bibliographies and were assessed in full. We excluded
221 90 studies: five reporting on the use of methotrexate, dinoprestone, mifepreistone alone,
222 laminaria, gemeprost (Autry *et al.*, 1999; Al Inizi and Ezimokhai, 2003; Johnson *et al.*, 1997;
223 Lelaidier *et al.*, 1993), 20 comparing different dosages, routes or formats of misoprostol
224 against each other, 15 non- or quasi-randomised, 16 not meeting the inclusion criteria and 34
225 not reporting the primary outcome. In total 46 randomised trials reporting on 9250 women
226 were included, of these two were in Portuguese (Holanda *et al.*, 2003; Pereira *et al.*, 2006)
227 and one in Norwegian (Karlsen, Jørn-Hugo; Hjalmar, 2001) (Figure 1).

228 A third of included trials were conducted in European countries (14/46, 30.4%) and fourteen
229 in Asian countries (14/46, 30.4%). Most studies included a two arms comparison and four
230 included three arms. The median study sample size was 60 (range 12-402). The majority of
231 trials were conducted in tertiary healthcare settings (35/46, 76.1%). One study was conducted

232 in outpatient settings. Eight were multicentre randomised trials (8/46, 17.3%). Table I
233 provides a summary of the characteristics of included trials.

234

235 ***Risk of bias***

236 The quality of included studies was overall moderate with some studies demonstrating a high
237 risk of bias (Supplementary Figure S1). Nine studies had a high risk of bias for randomisation
238 (9/46, 19.5%) and ten (10/46, 21.7%) had a high risk of bias for allocation concealment.
239 Outcomes assessment (i.e. attrition) was judged to have a high risk of bias in six studies, and
240 was inadequate in 15 studies (15/46, 32.6%) but good in 25 studies (25/41, 60.9%). Six
241 studies had a high risk of bias for detection (i.e. selective reporting) (6/46, 13%) and 14 had a
242 high risk of bias in outcomes reporting (i.e. incomplete data) (14/46, 30.4%). Conflict of
243 interest was declared as not present in only seven studies (7/46, 15.2%) and was not reported
244 on in the remaining studies. Only four studies were double blinded and these were studies
245 comparing medical treatments to placebo (3/46, 6%) (Bagratee *et al.*, 2004; Blohm *et al.*,
246 2005; Lister *et al.*, 2005; Sinha *et al.*, 2018). A summary of risk of bias assessment on
247 included trials is provided in Supplementary Table SII.

248

249 ***Primary outcome***

250 Our network for the primary outcome included 46 randomised trials (9250 women)
251 comparing seven treatment options: expectant management (EXP)(19 trials, 1587 women),
252 sharp dilation and curettage (D+C)(5 trials, 247 women) , electric vacuum aspiration under
253 general anaesthesia (EVAC)(19 trials, 1766 women), manual vacuum aspiration under local
254 anaesthesia (MVA)(12 trials, 1671 women), misoprostol alone (MISO)(32 trials, 3017
255 women), mifepristone + misoprostol (MIFE+MISO)(9 trials, 932 women), sequential

256 misoprostol + electric vacuum aspiration under general anaesthesia (MISO+EVAC)(1 trial,
257 30 women) (Figure 2).

258 Both direct and mixed evidence supported the overall inferiority of EXP compared to most
259 treatment options for achieving complete evacuation of products of conception (EXP vs
260 MISO RR 0.76, 95% CI 0.65-0.89; EXP vs EVAC RR 0.68, 95% CI 0.59-0.79; EXP vs D+C
261 RR 0.73, 95% CI 0.57-0.94; MISO+EVAC vs EXP RR 1.35, 95% CI 1.10-1.66; MVA vs
262 EXP RR 1.46, 95% CI 1.19-1.79) (Figure 3). All surgical treatments (MVA, EVAC and
263 D+C) demonstrated similar effectiveness for achieving the primary outcome. This was also
264 the case when comparing MISO against each of the surgical treatment options (MVA vs
265 MISO RR 1.10, 95% CI 0.92-1.33; EVAC vs MISO RR 1.11, 95% CI 0.97-1.27; D+C vs
266 MISO RR 1.03, 95% CI 0.82-1.30). Direct evidence on the use of MISO+EVAC was drawn
267 from one trial only (MISO+EVAC vs MISO, RR 2.86, 95% CI 1.45-5.64; data not shown)
268 and mixed evidence supports its superiority only over EXP (RR 1.35, 95% CI 1.10-1.66).

269 Mixed evidence did not support the use of MIFE+MISO compared to using MISO alone to
270 increase effectiveness (RR 1.43, 95% CI 0.87-2.36). However, we detected significant
271 inconsistency between direct and mixed evidence for MISO vs MISO+EVAC; EVAC vs
272 MISO; EVAC vs EXP; EVAC vs MIFE+MISO and EXP vs MISO (Supplementary Table
273 SI). The overall by network inconsistency analysis was significant at $p=0.003$. Adjusting for
274 inconsistency, mixed evidence favoured the addition of MIFE to MISO to improve
275 effectiveness (MIFE+MISO vs MISO RR 1.49, 95% CI 1.09-2.03) in contrast to
276 MISO+EVAC vs MISO (RR 0.63, 95% CI 0.51-0.79) (Supplementary Figure S3).

277

278 The surface under the cumulative ranking curve for treatment effectiveness was highest for
279 MIFE+MISO (SUCRA 89.3%) followed by EVAC (SUCRA 76.2%). EXP was ranked as the
280 least effective treatment (SUCRA 24%) (Figure 4). Visual analysis of our funnel plot

281 demonstrates a reasonable distribution of effect size with limited evidence of small study
282 effect (Supplementary Figure S4).

283

284 *Secondary outcomes*

285 Meta-analysis of mixed evidence demonstrated no difference for any of the following
286 outcomes between medical and surgical treatment options: need for blood transfusion, post-
287 treatment infection, serious complications, diarrhoea, vomiting, nausea and fever
288 (Supplementary Figures S5-11). Compared to MISO, MIFE+MISO was associated with a
289 lower risk ratio for developing fever (RR 0.33, 95% CI 0.19-0.57), nausea (RR 0.42, 95% CI
290 0.24-0.72) and vomiting (RR 0.55, 95% CI 0.32-0.94). Fewer women needed analgesia post
291 treatment in the EVAC group compared to MISO (RR 0.43, 95% CI 0.27-0.68). Those who
292 opted for EXP also used more analgesia compared to EVAC (RR 2.07, 95% CI 1.25-3.41)
293 (Supplementary Figure S12). Women's satisfaction was similar for all the treatment options
294 (Supplementary Figure S13). Supplementary Table SIII provides a summary of effect
295 estimates for all secondary outcomes across treatment options.

296

297 Table II summaries the calculated SUCRA and mean rank for the secondary outcomes by the
298 treatment options. Generally, MIFE+MISO had high ranking (low likelihood) for causing
299 common gastrointestinal (GI) side effects (nausea (SUCRA 93.1%), vomiting (SUCRA 84%)
300 and diarrhoea (SUCRA 63.2%)) and fever (SUCRA 86.8%). MVA had higher ranking (low
301 likelihood) for post-treatment infection (SUCRA 87.6%) and serious complications (SUCRA
302 79.2%) with the highest likelihood for post-treatment satisfaction (SUCRA 98%). Women
303 opting for EVAC had higher likelihood of requiring post-treatment blood transfusion
304 (SUCRA 14.7%).

305

306 **Discussion**

307 ***Main findings***

308 Our comprehensive meta-analysis showed that for managing first-trimester miscarriage, EXP
309 had lower effectiveness to achieve complete evacuation of products of conception compared
310 to other treatment options. Overall, there was similar effectiveness for the medical
311 (MIFE+MISO and MISO) and the surgical options (MVA, D+C, and EVAC), with similar
312 safety profiles reported. There was limited evidence to support the use of MISO+EVAC with
313 no information on its safety profile. Evidence on the use of MIFE+MISO suffered from
314 significant inconsistency. Overall, the addition of MIFE to MISO seems to improve its
315 effectiveness with reduced likelihood of side effects but more research is needed to address
316 the perceived inconsistency between direct and indirect evidence. Women's satisfaction was
317 similar for all the options compared.

318
319 Currently, EXP is recommended as the first-line treatment option for first-trimester
320 miscarriage (The National Institute for Health and Care Excellence, 2012). Women opting for
321 this approach should be counselled objectively about the chances of needing further
322 treatment, potential complications such as requiring blood transfusion (SUCRA 36.3%) or
323 more analgesia (SUCRA 37.4%), and the availability of other effective treatment options.
324 Excessive bleeding and repeated blood transfusion contribute to prolonged hospital stays and
325 long-term adverse outcomes such as alloimmunisation (Royal College of Obstetricians and
326 Gynaecologists, 2015) which are infrequently assessed in randomised trials.

327

328 ***Strength and limitations***

329 This review, to our knowledge, is the first to provide a comprehensive evidence synthesis
330 with network meta-analysis on all current treatment options for first-trimester miscarriage.

331 We conducted a systematic review of the literature with no search limitations. We assessed
332 and found little evidence of small study effect with the funnel plot analysis raising confidence
333 in our findings. We assessed the risk of bias using the Cochrane risk of bias assessment tool
334 (Higgins *et al.*, 2011) which demonstrated low to moderate risk of bias in the majority of
335 included studies. Compared to previously conducted meta-analysis (Nanda *et al.*, 2006;
336 Neilson *et al.*, 2006, 2013; Sotiriadis *et al.*, 2005; Wen *et al.*, 2008), our study provides
337 higher confidence supporting the role of medical treatment options for first trimester
338 miscarriage, incorporating indirect evidence and ranking treatments likelihood for
339 effectiveness and side effects.

340

341 Our findings are not without limitations. We were unable to accommodate for potential effect
342 modifiers such as variation in population characteristics relevant to age, parity, size of
343 products of conception, presence of side effects before randomisation and treatment settings.
344 A large gestation sac might require a higher doses of MISO to achieve complete evacuation
345 (Neilson *et al.*, 2006). Evidence on some treatment options, such as MVA, was sought
346 primarily from low/middle income countries, which could suggest variations in local practice
347 and geographical bias to one treatment option over the others.

348

349 There were variations in the ultrasound criteria used to diagnose the type of miscarriage
350 (missed vs incomplete) and the primary outcome of complete evacuation of products of
351 conception. The use of a standardised ultrasound criteria for the diagnosis of miscarriage is
352 only recent and some of the included trials pre-date the currently established guidelines
353 (The National Institute for Health and Care Excellence, 2012). To be pragmatic, we opted to
354 keep those trials and offer a comprehensive and accurate review of the available literature.
355 Similarly, there was variation in the type of included miscarriages (missed vs incomplete) in

356 each trial with some trials randomising either or both or simply not reporting on it (Table 1).
357 Due to the risk of inconsistency, we were unable to generate evidence on the management of
358 each type of miscarriage and our findings remain pragmatic. Such variation could be best
359 addressed using an individual participant data meta-analysis.

360

361 There was inconsistency within the network (Supplementary Table SI) specifically within
362 evidence loops comparing MIFE+MISO to other treatment options. We were unable to
363 attribute this inconsistency to a particular effect modifier and adjusted for it using established
364 models. Inconsistency could be attributed to the variations in the dosages and the routes of
365 administration of MISO among included trials. Typically, MISO is used in sequential doses
366 of 200 mcg and stopped once complete evacuation of products is achieved; this could present
367 inherent inconsistency among trials. Quality evidence on the most effective dose with the
368 least side effect is yet to emerge (Neilson *et al.*, 2006).

369

370 Variations in defining endpoints and the follow-up period limited the information on
371 important long term outcomes such as uterine adhesions, pre-term birth and future fertility.
372 Recent evidence suggest an increased risk for pre-term birth with multiple dilation and
373 curettage (Lemmers *et al.*, 2015). Future work should focus on following up randomised
374 cohorts to capture such outcomes.

375

376 To be pragmatic, evidence on MISO+EVAC, sought from one trial (Fang *et al.*, 2009), was
377 kept within our network in view of its wide use in current practice. The findings of this trial
378 should be interpreted with caution due to its small sample size, moderate risk of bias and
379 limited reporting on secondary outcomes. We planned to report on four additional outcomes

380 in our protocol (hospital stay, changes in haemoglobin, anxiety, and depression). This,
381 however, was not possible due to the large variability in reported end points.
382 We judged blinding to be possible in seven studies (Bagratee *et al.*, 2004; Blohm *et al.*, 2005;
383 Herabutya and O-Prasertsawat, 1997; Lister *et al.*, 2005; Ngai *et al.*, 2001; Nielsen *et al.*,
384 1999; Wood and Brain, 2002). Of these, only four (Bagratee *et al.*, 2004; Blohm *et al.*, 2005;
385 Lister *et al.*, 2005; Sinha *et al.*, 2018) were blinded, introducing a potential risk of bias. Lack
386 on information on blinding for outcomes assessment is another limitation in the included
387 studies.

388

389 ***Interpretation of findings***

390 Our study supports the use of medical treatments as a potential substitute for surgery,
391 however, studies to establish the lowest effective dose of MISO are needed (Neilson *et al.*,
392 2006). A higher dose of MISO is likely to cause more side effects such as nausea and
393 vomiting (Tang *et al.*, 2007). Medical management could be considered as a cost-effective
394 first-line treatment option. The woman's preference is an important factor to consider when
395 offering the various treatment options, often influenced by their carer's advice. There was
396 seldom consideration in the included studies for reporting outcomes important to the women
397 undergoing miscarriage, such as post-treatment anxiety and depression. None of the included
398 studies reported on the tolerability of each treatment option which can aid women to identify
399 their preferred choice. Developing a core outcome set with input from all stakeholders should
400 be considered in future research (Khan, 2016).

401

402 Recently, MIFE has been more commonly combined with MISO to improve the effectiveness
403 of medical treatment for uterine evacuation (Spitz *et al.*, 1998). Our analysis, seeking direct
404 and mixed evidence, suggests some added value compared to using MISO alone for first-

405 trimester miscarriage but with limited confidence due to the perceived inconsistency among
406 included trials. Considering its high cost, a cost-effectiveness evaluation is needed to
407 establish the value of using MIFE+MISO routinely. Using MISO for priming the cervix
408 before EVAC has been suggested to reduce the need for dilation and trauma to the
409 endometrium (Lawrie *et al.*, 1996). Evidence to support the effectiveness and safety of this
410 practice for managing first trimester miscarriage is scarce (only one randomised trial of 75
411 women) (Fang *et al.*, 2009) and more trials are needed to justify the potentially increased cost
412 and side effects.

413

414 Outpatient use of MVA with direct access to operating theatres could offer cost reduction
415 (Magotti *et al.*, 1995). While EXP is arguably cheaper than other treatment options, the
416 higher probability of complications might increase its associated cost. There is a need for a
417 comprehensive economic evaluation with extended decision models to accommodate for the
418 effectiveness of all available treatment options and potential adverse outcomes (Strand,
419 2015). Comprehensive policymaking including all available treatment options could offer
420 better value for money and facilitate higher patient satisfaction (Dalton *et al.*, 2015; Molnar *et*
421 *al.*, 2000; Wallace *et al.*, 2010) (Supplementary Figure S2).

422

423 Our study provides important insight for various stakeholders involved in caring for women
424 with first trimester miscarriage. Future work should aim to involve stakeholders' views
425 prospectively on relevant health outcomes to provide safe and cost-effective care. Efforts to
426 standardise treatment options and reduce selective reporting of outcomes are warranted to
427 reduce inconsistency in evidence synthesis.

428

429 **Conclusions**

430 Medical treatments for first-trimester miscarriage have similar effectiveness and side effects
431 compared to surgery. The addition of MIFE could increase the effectiveness of MISO and
432 reduce side effects though evidence is limited due to inconsistency. EXP has lower
433 effectiveness compared to other treatment options.

434

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438

439 **Authors' roles:**

440 BHA conceived the idea, performed the search, extracted data and wrote the first draft. NM
441 extracted data; AT and JZ performed the analysis and revised the manuscript; KSK revised
442 the manuscript and supervised the study. All authors provided critical input to the final
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453 **Figures and tables legends:**

454 **Figure 1: The study selection process for network meta-analysis on management of first**
455 **trimester miscarriage.**

456

457 **Figure 2: Network of treatment options for first trimester miscarriage.** Options:

458 expectant management (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration

459 (EVAC), manual vacuum aspiration (MVA), misoprostol alone (MISO),

460 mifepristone+misoprostol (MIFE+MISO) or misoprostol+electric vacuum aspiration

461 (MISO+EVAC).

462 The size of the dots represents the number of women randomised to each treatment option

463 and the thickness of the lines represents the number of randomised trials with head to head

464 comparison between each two treatment options.

465

466 **Figure 3: Direct (D) and mixed (M) evidence meta-analysis for treatment options for**

467 **first trimester miscarriage.** Options: expectant management (EXP), sharp dilation and

468 curettage (D+C), electric vacuum aspiration (EVAC), manual vacuum aspiration (MVA),

469 misoprostol alone (MISO), mifepristone+misoprostol (MIFE+MISO) or misoprostol+electric

470 vacuum aspiration (MISO+EVAC).

471

472 **Figure (4): The mean rank and cumulative rank probability (SUCRA) of effectiveness**

473 **for each treatment option for first trimester miscarriage.** Options: expectant management

474 (EXP), sharp dilation and curettage (D+C), electric vacuum aspiration (EVAC), manual

475 vacuum aspiration (MVA), misoprostol alone (MISO), mifepristone+misoprostol

476 (MIFE+MISO) or misoprostol+electric vacuum aspiration (MISO+EVAC).

477 Treatments with the top mean rank and the largest area under the curve have the highest
478 probability of achieving the primary outcome of complete evacuation of products of
479 conception.

480

481 **Table I: Characteristics of included trials evaluating treatment options for first**
482 **trimester miscarriage.**

483

484 **Table II: Summary of the calculated mean rank and the surface under the cumulative**
485 **ranking curve (SUCRA) for the secondary outcomes for the treatment options for first**
486 **trimester miscarriage.**

487 Treatments ranked first have lower likelihood to achieving adverse outcomes and higher
488 likelihood of post-treatment satisfaction. Treatments with a higher SUCRA score have lower
489 likelihood of achieving adverse outcomes and higher likelihood of post-treatment
490 satisfaction.

491

492 **Supplementary Figure S1: Risk of bias in included trials on the treatment options for**
493 **first trimester miscarriage.**

494

495 **Supplementary Figure S2: Flow chart for the management of women with first**
496 **trimester miscarriage.**

497

498 **Supplementary Figure S3: Mixed evidence meta-analysis adjusted for inconsistency for**
499 **treatment options for first trimester miscarriage.**

500

501 **Supplementary Figure S4: Funnel plot of the treatment effect for included trials on**
502 **treatment options for first trimester miscarriage.**

503

504 **Supplementary Figure S5: Mixed evidence network meta-analysis of blood transfusion**
505 **following treatment options for first trimester miscarriage. (A) Network map. (B) Forest**
506 **plot. (C) SUCRA.**

507

508 **Supplementary Figure S6: Mixed evidence network meta-analysis of infection/pelvic**
509 **inflammatory disease following treatment options for first trimester miscarriage. (A)**
510 **Network map. (B) Forest plot. (C) SUCRA.**

511

512 **Supplementary Figure S7: Mixed evidence network meta-analysis of serious**
513 **complications following treatment options for first trimester miscarriage. (A) Network**
514 **map. (B) Forest plot. (C) SUCRA.**

515

516 **Supplementary Figure S8: Mixed evidence network meta-analysis of diarrhoea**
517 **following treatment options for first trimester miscarriage. (A) Network map. (B) Forest**
518 **plot. (C) SUCRA.**

519

520 **Supplementary Figure S9: Mixed evidence network meta-analysis of vomiting following**
521 **treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C)**
522 **SUCRA.**

523

524 **Supplementary Figure S10: Mixed evidence network meta-analysis of nausea following**
525 **treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C)**
526 **SUCRA.**

527

528 **Supplementary Figure 11: Mixed evidence network meta-analysis of fever following**
529 **treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C)**
530 **SUCRA.**

531

532 **Supplementary Figure 12: Mixed evidence network meta-analysis of analgesia following**
533 **treatment options for first trimester miscarriage. (A) Network map. (B) Forest plot. (C)**
534 **SUCRA.**

535

536 **Supplementary Figure 13: Mixed evidence network meta-analysis of women's**
537 **satisfaction following treatment options for first trimester miscarriage. (A) Network**
538 **map. (B) Forest plot. (C) SUCRA.**

539

540

541 **Supplementary Table SI: Side-split analysis of inconsistency in the network of**
542 **treatment options for first trimester miscarriage.**

543

544 **Supplementary Table SII: Summary of risk of bias for included studies.**

545

546 **Supplementary Table SIII: League table of effect estimates for secondary outcomes**
547 **across treatment options for first trimester miscarriage.**

548

549

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