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Mediterranean diet based intervention in pregnancy to improve maternal and fetal outcomes: Methodological challenges and lessons learned from the multicentre ESTEEM study

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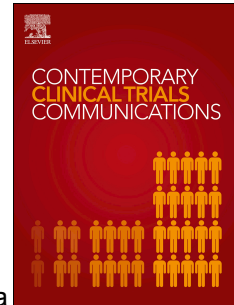
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1 **Mediterranean diet based intervention in pregnancy to improve maternal and fetal**
2 **outcomes: Methodological challenges and lessons learned from the multicentre**
3 **ESTEEM study**

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31

32 **Key words:** Mediterranean diet, randomised trial, pregnancy, obesity

33 **Abstract:**

34 **Introduction:** Evaluating complex dietary interventions such as Mediterranean diet in
35 pregnancy presents unique methodological challenges. We present the challenges and the
36 lessons learned from a multicentre randomised trial (ESTEEM) on Mediterranean-based
37 dietary intervention in pregnancy.

38 **Methods:** We recruited pregnant women who met our predefined inclusion criteria and
39 randomised those with metabolic risk factors to the Mediterranean-based dietary intervention
40 or routine antenatal care. We evaluated the effect of the ESTEEM intervention on composite
41 maternal and fetal outcomes.

42 **Challenges and solutions:** The main challenges were encountered in recruiting to ESTEEM,
43 delivering the intervention, engaging clinical staff, assessing adherence and choosing the
44 outcome measures. The large sample size coupled with the slow recruitment rate forced us to
45 extend the recruitment period by 4 months. The limitation in available resources was
46 overcome by opening sites in a step-wise approach. Engaging healthcare providers was
47 promoted by embedding the recruitment and the follow-up activities into current clinical
48 practice, and promoting research skills training. We delivered the intervention early on in the
49 pregnancy to promote the dietary effect on healthy placentation and reduce metabolic risk
50 factors. Participants and their families were actively involved in the dietary intervention to
51 improve adherence through a series of group teaching sessions. A user-friendly short dietary
52 questionnaire was developed and validated to assess adherence to the intervention. The trial
53 composite primary outcome was chosen in consensus based on input from a panel of experts.

54 **Conclusion:** The ESTEEM experience offers an insight into future pragmatic nutritional
55 studies in pregnancy.

56

57 Introduction:

58 Women with metabolic risk factors such as high BMI, dyslipidaemia and chronic
59 hypertension are at increased risk of developing adverse outcomes such as gestational
60 diabetes, pre-eclampsia and admissions to neonatal intensive care units.(1) With the rapidly
61 increasing number of women entering pregnancy as obese or overweight, researchers are
62 more focused on evaluating the role of dietary and lifestyle interventions to improve maternal
63 and fetal health outcomes.(2)

64

65 Mediterranean based diet has been shown to improve cardiovascular outcomes in a non-
66 pregnant population.(3,4) The effect of such diet on pregnancy outcomes in women with
67 metabolic risk factors is not known.(5,6) Evaluating complex dietary interventions such as
68 those based on Mediterranean diet in a pregnant population poses unique methodological and
69 conceptual challenges.(7,8) The lack of standardised, and accepted methods to evaluate the
70 effectiveness of dietary interventions may lead to inconsistent findings in nutritional
71 epidemiology. Factors such as participants' adherence to the intervention and the accuracy of
72 the dietary assessment methods could also affect the study findings.(9)

73 We undertook a multicentre randomised trial (ESTEEM) to assess the effectiveness of a
74 Mediterranean based diet intervention to reduce complications in pregnant women with
75 metabolic risk factors. In this article we highlight the methodological challenges and the
76 lessons learned from the ESTEEM study.

77

78 Methods:

79 *Study design*

80 ESTEEM is a randomised trial embedded in a cohort study. Recruitment started in September
81 2014 and finished in February 2016 in five tertiary maternity units in the UK (covering
82 30,000 deliveries per year). We included pregnant women who met the following criteria: at
83 least 16 years of age, BMI between 18.5 Kg/m² and 40 Kg/m², singleton pregnancy of 18
84 weeks gestation or less, good understanding of written and spoken English, able to consume
85 nuts and olive oil and follow a Mediterranean diet lifestyle. We randomised eligible women
86 with metabolic risk factors (raised serum triglycerides (≥ 1.7 mmol/L), obesity (BMI ≥ 30
87 Kg/m²), or chronic hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic blood
88 pressure)) to the ESTEEM dietary intervention or routine antenatal dietary care. Participants
89 with no metabolic risk factors were followed up in the cohort group and only outcome data
90 were collected (Figure 1). The primary outcome is a composite maternal outcome defined as
91 pre-eclampsia (new onset or superimposed) or gestational diabetes; and a fetal composite
92 outcome defined as stillbirth, small for gestational age fetus (birth weight less than 10th
93 centile) or admission to the neonatal intensive care unit. The full protocol of the ESTEEM
94 study has been reported previously (10).

95

96 The ESTEEM dietary intervention is based on Mediterranean diet lifestyle with education to
97 modify lifestyle choices. The key components of the diet included high intake of fruit and
98 vegetables, non-refined grains, legumes; moderate to high consumption of fish; small to
99 moderate intake of poultry and dairy products such as yoghurt and cheese; low consumption
100 of red meat and processed meat and avoidance of sugary drinks, fast food and food rich in
101 animal fat. In particular, ESTEEM promoted high intake of nuts (including walnuts,
102 hazelnuts, and almonds estimated at 30 g/day) and high intake of extra virgin olive oil as the
103 main source of fat (estimated at 0.5 L/week). The intervention also included dietary education

104 sessions, grocery shopping advice, cooking recipes for a healthy diet and advice for
105 appropriate meal choices at restaurants.

106 Randomised participants were also consented to collect umbilical cord samples after delivery
107 to be used for future research on the effect of the dietary intervention on fetal biochemical
108 outcomes.

109

110 We expected the ESTEEM dietary intervention to reduce the incidence of the composite
111 primary outcome by 30%, assuming a 24% background risk in our population. Allowing for
112 a 20% dropout, the sample size required is 1230 eligible women to ensure an 80% power at
113 the 5% significance level for maternal and fetal composite outcomes. ESTEEM has
114 completed its recruitment and currently in the follow up phase.

115

116 **Challenges and solutions**

117 *Recruitment*

118 The initially planned recruitment period was 14 months. However, this was proven to be
119 insufficient after the pilot phase given the large sample size required and the slower than
120 expected recruitment rate. After discussion with the trial steering committee (TSC) we
121 resolved to extend the recruitment period by further four months, and increased the number
122 of recruitment centres from three to five major tertiary maternity units in the UK (4 in
123 London and 1 in Birmingham). We opened sites in a step wise approach, which enabled us to
124 test and troubleshoot recruitment challenges at each site prior to opening another site. This
125 allowed us to allocate the trial resources judiciously and to factor in the relatively long

126 intervention and follow up periods for each participant.(11) The recruitment centres were
127 closed in a similar fashion based on a forecast of recruitment figures and staff allocation.

128

129 We implemented a series of evidence-based measures designed to embed the trial recruitment
130 and follow-up process into clinical practice at the ESTEEM sites.(12) We provided research
131 training to clinical midwives in groups and individually with the objective to enable them to
132 recruit and consent participants alongside routine antenatal care. Clinical staff engagement in
133 ESTEEM was promoted with a series of talks and interactive teaching sessions on the
134 benefits of involving patients in research studies. We recognised the contribution of our top
135 recruiting midwives at each of the sites with acknowledgment certificates, dissemination in
136 newsletters and research meetings, and awarded small financial incentives. We attached an
137 additional ESTEEM eligibility sheet to all booking clinical notes to remind clinical staff to
138 recruit booking women. A team of dedicated research staff provided daily support in the
139 antenatal clinics to help screen and recruit women at their booking visit. Participants who
140 required additional time to consider the trial before consenting were followed up with
141 telephone calls by our team. Overall clinical midwives consented a third of participants
142 recruited into ESTEEM.

143

144 *Intervention*

145 In ESTEEM, we focused on delivering the intervention early in the pregnancy to promote the
146 dietary effect on healthy placentation and reduce metabolic risk factors. We initially planned
147 to deliver the intervention by 18 weeks gestation. However, this was not always possible, as
148 many participants were not able to attend their initial appointment. Taking a pragmatic
149 approach, and reflecting on clinical practice, following our pilot phase we decided to extend

150 the intervention window till 20 weeks gestation. This ensured that participants who were
151 attending for their 20 weeks detailed ultrasound scan were involved in the intervention
152 delivery process.

153

154 *Engagement*

155 Participants' beliefs and food culture are major confounders in such trials particularly in
156 pregnant women.(13) Engaging participants in the planning of the intervention is advised to
157 ensure higher adherence to the intervention.(14) Traditionally, women are advised to "eat for
158 two" and the health benefits of certain food groups are overrated.(15) Mothers are also more
159 likely to follow advice from peers, partners and family members compared to health care
160 professionals.(16) We actively involved our participants in the design and the implementation
161 of the required dietary changes. Dietary interventions based on the social cognitive theory
162 have been shown to be effective to improve compliance.(17) Building on this, we delivered a
163 number of educational sessions to boost the participants' knowledge on nutrition in
164 pregnancy on topics such portion sizes and the benefits of Mediterranean diet to both mother
165 and baby. We also prompted participants to share experiences and success stories with each
166 other to improve adherence to the intervention. Additionally, we involved partners and the
167 whole family where possible to improve adherence particularly in larger families where
168 pregnant women may not do the shopping and the cooking for the entire household. We
169 encouraged participants to set personalised goals based on the SMART model (specific,
170 measurable, achievable, relevant and time specific) to create a personalised working plan and
171 implement the recommended dietary changes in their lifestyle.

172

173 purchasing extra virgin olive oil and nuts may be too expensive to some of our participants in
174 the intervention group, which could affect adherence.(18) We tackled this by providing
175 regular supply of extra virgin olive oil to cook for the whole family, and sachets of nuts
176 (walnuts, hazelnuts, and almonds) for personal use throughout the pregnancy.

177

178 We planned the following two intervention sessions (at 20 and 28 weeks) in a group setting
179 for both the participants and their partners. The aim of these sessions was to provide further
180 knowledge on the benefits of Mediterranean diet, healthy shopping habits, reading food labels
181 and beneficial food for the baby. The sessions also aimed to support the participants by
182 exploring obstacles arising and sharing experiences.(16) Planning these sessions was not
183 always possible in a group setting and often took place with only one or two participants. For
184 those participants who missed a session or two we attempted to reschedule or arranged to
185 send them the nuts and extra virgin olive oil by post to ensure they maintain their intake and
186 compliance with the intervention.

187

188 *Assessing adherence to dietary intervention*

189 Accurate estimation of participants' basal dietary intake was required before introducing the
190 intervention.(7) We therefore used the multi-pass 24 hour dietary recall technique combined
191 with a series of focused questions to carefully assess the participant's dietary habits at
192 baseline.(19) This helped our dieticians to identify areas for improvement and the necessary
193 changes towards adopting a Mediterranean based diet.

194

195 Our population consisted mainly of multiparous women, often from a transiently immigrant
196 background. Many of our participants had low literacy of English language, and had
197 difficulties to complete a complex tool such as weighted food diaries.(20) Using such a
198 labour intensive tool was particularly not ideal for the majority of our participants looking
199 after large families and in full time employment.(8) Since our main objective was to
200 primarily quantify the participants' adherence to the planned intervention we decided to use a
201 short 12 items food questionnaire focused that captured the main elements of a Mediterranean
202 diet (The ESTEEM Q).

203

204 We adapted the ESTEEM Q from a similar questionnaire that was validated in a
205 Mediterranean non-pregnant population.(21) We amended the our questionnaire by removing
206 two questions that were not applicable to our population (alcohol intake and sofrito, a tomato
207 sauce made of a combination of tomato, olive oil, garlic, and onion) consumption) and added
208 7 dichotomous questions to investigate conditions specific to pregnancy that could affect the
209 participants' dietary intake. We used a point scoring scale to assess adherence to the
210 Mediterranean diet based intervention using previously validated cut-off values. (22)

211 We intended to use the number of retained empty packets of nuts and extra virgin olive oil as
212 a marker of participants' consumption. However, we aborted the use of this method due to
213 poor returns. The use of specific biomarkers such as alpha-linolenic acids for nuts intake and
214 hydroxytyrosol for olive oil was another possibility to objectively assess nutrients'
215 intake.(23) Using biomarkers has a number of limitations; they are expensive, invasive and
216 provide only a snap shot view of the dietary consumption.(23) Taking into account the extra
217 cost required, we opted to drop the use of biomarkers.

218 Given the above limitations we decided to assess the adherence to the intervention by
219 evaluating the number of attended intervention sessions and comparing the scores obtained
220 from the ESTEEM Q.

221

222 *Control group*

223 Selecting appropriate control subjects in dietary trials is often challenging in clinical settings
224 (24). There is no clear guideline on what constitute a suitable control population for
225 interventional dietary studies in pregnancy. In line with ESTEEM's pragmatic design, we
226 decided to not impose any dietary requirement on our control group and provided usual
227 antenatal care as per the national guidelines within the national health service. (25)

228

229 The pragmatic design of ESTEEM provides higher external validity to assess the
230 effectiveness of the dietary intervention. Our population has diverse ethnic backgrounds with
231 different food cultures, some of whom might be adopting a Mediterranean lifestyle already.
232 Many participants were from transiently immigrant families with likely varying food habits.
233 This could affect the validity of comparing dietary outcomes between the two groups

234

235 *Assessment of outcomes*

236 ESTEEM was designed as a pragmatic trial to assess the effectiveness of dietary intervention
237 on composite maternal and fetal outcomes in clinical practice. We used a robust method to
238 identify the components of the composite outcome based on a multi-stage modified Delphi
239 survey of clinical and academic experts in obesity research in pregnancy.(26) Both pre-
240 eclampsia and gestational diabetes were prioritised to be the most clinically important

241 maternal outcomes and were included in the composite primary outcome. Our panel of
242 experts identified stillbirth, small for gestational age fetus (birth weight less than 10th centile)
243 and admission to the neonatal intensive care unit to be the most clinically important
244 fetal/neonatal outcomes and were incorporated into the composite outcome. We also decided
245 to report on each of these outcomes individually as secondary outcomes. Reporting on dietary
246 outcomes was restricted to the information collected in the ESTEEM Q.

247

248 Complete outcome collection after delivery was logistically challenging within the allocated
249 time window. We dedicate a research midwife to screen the labour and postnatal wards daily
250 for any ESTEEM patients in order to capture all new deliveries. We also crosschecked daily
251 hospital admission records against our electronic records of the participants estimated
252 delivery date to reduce loss to follow ups.

253

254 Collecting cord blood samples proved to be very demanding in terms of time and resources.
255 We sought help from clinical midwives on the delivery suite to assist in collecting and
256 reserving cord blood samples as per the ESTEEM protocol. We produced special ESTEEM
257 stickers on the participants' maternity notes and wall posters on delivery suit to remind our
258 midwives to collect the cord blood samples for eligible participants.(27)

259 Table (1) provides a summary of encountered challenges and applied solutions in ESTEEM.

260

261 **Discussion**

262 The notion that pregnancy could offer a unique window of opportunity to invoke change in
263 mothers' lifestyle has inspired many researchers in recent years. However, to date, the

264 recorded success remains limited.(5) This is often attributed to the poor quality of available
265 evidence and small sample sizes. Methodological deficiencies affect the effect size and the
266 transferability of trial findings into clinical practice. Elements such as the timing of
267 introducing the intervention in pregnancy, choice of population, compliance and dietary
268 assessment methods are all important factors to consider when designing diet based
269 interventional studies.(8)

270

271 The ESTEEM study was focused on evaluating the effectiveness of increased maternal intake
272 of unsaturated fatty acids early in reducing metabolic disorders in pregnancy namely
273 gestational diabetes and preeclampsia. The knowledge about the fatty acid disposition in
274 pregnancy and role of the placenta in the metabolic changes is still somewhat limited.(28)
275 Our theory is that a high intake of poly unsaturated fatty acids and mono unsaturated fatty
276 acids will improve the endothelial function, reduce oxidative stress and reduce insulin
277 resistance thus reducing metabolic risk factors. Obese mothers tend to develop higher
278 concentration of plasma lipids such as triglycerides and very low-density lipoprotein
279 throughout pregnancy. However, the levels of unsaturated fatty acids remain stable at pre-
280 pregnancy levels.(29) Altering the maternal diet could help to increase the levels of these
281 useful nutrients and amplify their role in reducing oxidative stress.(30) The design of the
282 ESTEEM study will provide pragmatic evidence on the role of Mediterranean diet in
283 improving pregnancy outcomes in clinical practice.

284

285 To date, our knowledge on the potential long term benefits of dietary intervention in
286 pregnancy remains limited, in contrast to the proven adverse effect of obesity on long term
287 maternal and childhood outcomes.(31,32) Nutritional studies should aim to engage

288 randomised postpartum cohorts in long term follow-up studies to evaluate long term health
289 outcomes and retention of the intervention after pregnancy.

290 The maintenance of the intervention in the population and the prevalence of healthy lifestyle
291 after the trial lifetime are also poorly investigated (5); often due to funding and resources
292 limitations. Advances in dietetics' technology could help to address this challenge in future
293 studies at low cost. The use of mobile apps and internet based interventions has been reported
294 to be helpful in maintaining diabetic control and other chronic diseases.(33,34) Such methods
295 could significantly help to gather more individualised and long term health outcomes.

296
297 Exploring the qualitative aspect in interventional trials is an important aspect to better
298 develop and implement lifestyle interventions is. Qualitative research can help to gather more
299 information on mothers views and attitude towards changing their lifestyle before, during and
300 after pregnancy.(35) This is particularly helpful to explore potential obstacles to changing
301 dietary habits in certain subgroups such as participants of low socio-economic status.(36)

302
303 Our knowledge about dietary interventions around pregnancy has evolved markedly in the
304 last few years. However, several methodological challenges still persist. Innovative and
305 creative research methods are needed to address this important public health issue.

306

307 **Conclusion:**

308 Dietary lifestyle interventions in pregnancy are associated with a number of methodological
309 challenges. The ESTEEM experience offers an insight into future pragmatic nutritional
310 studies in pregnancy.

311 **Trial registration number:** NCT02218931

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316

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321 Food Academy UK

322

323 **Conflict of Interest:**

324 All authors disclose no conflict of interest.

325

326 **Authors' contribution:**

327 BHA wrote the first manuscript draft and is helping with in the study conduct, JD, SH and

328 AP are co-ordinating the study conduct and drafted the protocol, EP is delivering the

329 intervention, RH and LE designed the statistical analysis plan, TR, MBR, GH and KSK

330 helped in developing the protocol, ST is the chief investigator for ESTEEM and overseeing

331 the study conduct. All authors provided critical input to the manuscript.

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Table (1): Summary of challenges and solutions proposed in the ESTEEM study.

Domain	Challenge	Solution
Recruitment	Large sample size and slow recruitment rate	Extended recruitment by 4 months and opened more recruitment centres.
		Engaged clinical staff in the recruitment and follow up process
		Assigned dedicated research staff to screen antenatal clinics daily
Delivery of the intervention	Poor attendance to initial intervention sessions	Extended the intervention window up to 20 weeks gestation
Participants engagement with the study	Various food cultures and dietary habits among participants Improve adherence to the intervention	Tailored intervention based on individual food habits assessment
		Actively engaged participants and their families in planning the required dietary changes to comply with the intervention
		Provided group dietary educational sessions
		Provided nuts and extra virgin olive oil throughout the pregnancy
Adherence to the intervention	Assessing basal dietary intake	Used of a multi-pass 24 hour dietary recall with focused questions
	Choice of dietary assessment tool	Developed and validated a user friendly short dietary questionnaire specific to Mediterranean diet
Control group	Choice of control participants	Adopted a pragmatic approach with no specific dietary requirement in the control group
Outcomes	Choice of primary outcome	Developed a composite outcome of maternal and fetal outcomes prioritised by a panel of experts.
	Complete outcome collection	Assigned dedicated research staff to screen postnatal and labour ward and crosscheck participants against electronic records

Figure (1): ESTEEM study design including the screening, recruitment and randomisation process.

