Prof Ben Mol, Nicole Au, Jessica Srivastava – Written evidence (PRT0075)

We were delighted to hear that the British parliament is addressing preterm birth prevention and its consequences. We strongly support the committee's decision to consider current evidence. We are writing you with a maybe unexpected concern. Unfortunately, medical science is compromised by untrustworthy randomised controlled trials (RCTs), with estimates of fatally flawed or even false circulating RCTs throughout medicine in the hundreds of thousands, about 30% of the total number of RCTs[1,2].

This is important recommendations to prevent preterm birth will be based on the medical literature, and these untrustworthy and even false RCTs will wrongly inform policy makers and other stakeholders. In view of increasing concerns about the trustworthiness of RCTs, a team of researchers from my department conducted a thorough review of the literature on the prevention of spontaneous preterm birth (<37 weeks). Our review led us to consider the trustworthiness of two meta-analyses published by the BMJ on the management of preterm birth. Care et. al.[3] compared the effectiveness of interventions to prevent spontaneous preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth or short cervical length (61 randomised control trials (RCTs)).[3] Saccone and Berghella[4] evaluated the effectiveness of antenatal corticosteroids in women delivering late preterm and term (6 RCTs).[4]

We used a standardized checklist (TRACT) to assess trustworthiness of RCTs[5]. Our review, as described in more detail below, demonstrates trustworthiness concerns in 12/61 studies (2721/17273 participants) in the review of Care et al.[3] and 3/6 studies in the Saccone[4] review (1779/5698 participants), with trustworthy studies generating a far more

conservative estimate of treatment effects than the untrustworthy studies.

We have detailed our findings in a letter that we are about to send to the BMJ. Our priority is that these trials should not be used to inform clinical practice. We share these concerns with you as these studies are still being cited widely[3,4]. Their trustworthiness has not before been considered and therefore, may contribute to guiding current clinical practice and the poor outcomes for neonatal morbidity and mortality associated with preterm birth. This issue is mostly ignored by the academic community and medical publishers, with attention coming from outside medicine (https://www.economist.com/science-and-technology/2023/02/22/there-is-a-worrying-amount-of-fraud-in-medical-research). While I had no time to discuss this letter in detail with colleagues, I am sure that prominent British colleagues like professors Andrew Shennan, Peter von Dadleszen and Jim Thornton support my concerns.

Introduction

In the last decade, the BMJ has published two meta-analyses on the management of preterm birth. Care et. al.[3] compared the effectiveness of interventions to prevent spontaneous preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth or short cervical length (61 randomised control trials (RCTs)).[3] Saccone and Berghella[4] evaluated the effectiveness of antenatal corticosteroids in women delivering late preterm and term (6 RCTs).[4]

The question of whether the data underlying these meta-analyses are trustworthy has not been addressed. Unfortunately, this question is relevant as untrustworthy RCTs are an increasing concern, with estimates of fatally flawed or even false circulating RCTs in the hundreds of thousands[1,2]. Alfirevic et al.[6] studied 375 RCTs included in 18 Cochrane

reviews and concluded that 95 RCTs (25%) of them merited exclusion, resulting in changes in 78% (14/18) of the reviews, including important differences in the conclusions of 33% (6/18)[6]. In view of the increasing concerns about the trustworthiness of RCTs, we assessed the trustworthiness of the studies underlying meta-analyses of Care et al. and Saccone et al.[3,4]

Methods

We used the TRACT checklist to assess trustworthiness[5]. The TRACT checklist covers 19 items across 7 main domains including 1) governance (3 items), 2) author group (2 items), 3) plausibility of intervention usage (2 items), 4) timeframe (3 items), 5) drop-out rates (2 items), 6) baseline characteristics (3 items), and 7) outcomes (2 items)[5]. Each item is rated as no concerns, some concerns, major concerns or no information[5]. If a study assessed were to have any of these parameters rated at a level of major concern[5], we considered the study's reported methodology, IPD and results to determine whether a trial was untrustworthy. For Care et. al.[3], we assessed if individual participant data (IPD) had been shared in the EPPPIC meta-analysis[7,8]. We also considered whether these trials appeared in the Cochrane database and were cited in Cochrane reviews.

Results For the 61 studies included in Care et. al.[3], the TRACT checklist scored positive on Governance (33%), Author group (25%), Timeframe (16%), Dropout Rate (28%), Baseline Characteristics (13%), Outcomes (46%) while in the domain Plausibility of Intervention Usage no studies were flagged (Table 1, Supplementary Tables 1 and 3). Based on the TRACT checklist, we classified 12 of the 61 studies as potentially untrustworthy as multiple items (including governance (9/12), author group (4/12), timeframe (4/12), dropout rate (7/12) and baseline characteristics (5/12)) were rated at a major concern level (Table 1) for these RCTs. The most common items of concern within the untrustworthy

trials included absence of registration (9 positive), zero participant dropouts (7 positive), and rounded participant numbers (6 positive) (Supplementary Table 3). Only one of these 12 RCT[15] did share IPD with EPPPIC, but was excluded from EPPPIC due to improper randomisation of its participants [7,8]. All trials except two[9,29] were in the Cochrane database[31-40] and all except four[9,24,27,29] were cited in Cochrane reviews, mostly in the Cochrane review by Dodd et al.[40]

A summary of the major concerns about these 12 potentially untrustworthy RCTs shows the following. Ahuja et al.[9] reported asymptomatic high risk singleton pregnancies without specifying 'high risk', with a cervical length reported in 20 of 80 participants. Akbari et. al.[10] is a meeting abstract by three authors that reported on recruitment of two times 75 women in a never published study. In Ashoush et al.[11] raw data indicated complete separation of progesterone values in the intervention and control groups[13], but editors of Acta Obstetricia et Gynecologica Scandinavica refused to take action against the paper[14]. Cetingoz et. al.[15] had shared data that were inconsistent with random allocation[7,8]. El-Gharib and El-Hawary[16] published with two authors study which, according to the title, is a matched sample comparison, the abstract states that patients were 'classified' into vaginal or intramuscular progesterone, while the main text described a 'randomised, double-blind (by sealed envelopes) trial'. It is not explaining that a placebo-controlled study evaluating vaginal and intramuscular drug requires two placebos[16]. The first author of Ibrahim et. al.[17] has three papers retracted [18,19,20], while Maher et al.[22] has been retracted[22,23]. Jabeen[24] (2012) recruited 60 participants between November 1st and December 31st 2011, with the paper, after an unknown submission date, published early 2012. Karbasian[25] conducted an unregistered RCT, involving two other authors (M. Sheikh & S. Hantoushzadeh), with the second author[25,26] having a retracted paper in 2016. Furthermore, the authors conducted two RCTs on preventing preterm birth simultaneously, during the same timeframe.

Pirijani[27], a co-author of Karbasian[25], reported findings from a study that largely overlapped with Karbasian's timeframe, despite being presented as an independent study[27]. Saghafi[28] reported zero dropouts and rounded participant numbers. Wajid[29] recruited 800 participants between March and December 2015, with a submission on 29 March 2016.

Our assessment of the six RCTs included in the meta-analysis from Saccone et al.[2] (Table 2, Supplementary Tables 2 and 4) was positive on Governance (1/6), Author group (2/6), Timeframe (2/6), Dropout Rate (2/6), and Outcomes (2/6) while Baseline Characteristics and Plausibility of Intervention Usage did not flag any issues. We classified three of the six studies as potentially untrustworthy based on the TRACT checklist as multiple items (including governance (1/3), author group (2/3), timeframe (2/3) and dropout rate (2/3)) were rated at a major concern level (Table 2). The most common items of concern within the untrustworthy trials included fast submission (2 positive), zero participant dropouts (2 positive) and rounded participant numbers (1 positive) (Supplementary Table 4).

Ahmed[41] (2015) is a copy of an earlier study by the same author on the same topic, with all numbers doubled[41]. This also explains why Ahmed et al. only has even numbers. This article has an expression of concern since September 2023[42]. Balci[43] (2010) had zero dropouts and rounded participant numbers and was submitted implausibly fast (trial concluding May 2009 and submitted July 2009). Nada[44] (2016) has since been retracted.

Consequence of exclusion of the untrustworthy RCTs We repeated the network meta-analysis for preterm birth prevention considering only studies deemed trustworthy while we also analysed trustworthy studies. This allowed us to compare how treatment effect estimates varied between the two groups of studies. For the vaginal progesterone treatment, 38 trustworthy studies reported on preterm birth <37 weeks and yielded an odds ratio of 0.67 (95% CI: 0.45 to 0.99). In contrast, ten

untrustworthy studies reporting on this <37 weeks outcome estimated the odds ratio to be 0.30 (95% CI: 0.18 to 0.49) (Table 5). The comparison of the treatment with intramuscular progesterone (17OHPC) shows a similar discrepancy between trustworthy studies (OR=0.64, 95% CI 0.44 to 0.93) and non-trustworthy studies (OR=0.39, 95% CI: 0.22 to 0.69)). This suggests that, in a rough sense, the effect estimated by the untrustworthy studies is more than two times stronger than that estimated by the trustworthy studies.

In our repeated meta-analysis using the six RCTs originally included in Saccone et al. we derived an overall odds ratio of 0.55 (95% CI 0.33 to 0.93). For the three untrustworthy studies, the odds ratio was 0.29 (95% CI: 0.19 to 0.45) while for the three trustworthy studies this was 0.79 (95% CI 0.55 to 1.13). Similarly, as for prevention of preterm birth, the odds ratios estimated from the untrustworthy studies indicated a considerably stronger treatment effect in those untrustworthy studies.

Conclusion

Our review found trustworthiness concerns in 12/61 studies (2721/17273 participants) in the review of Care et. al.[3] and 3/6 studies in the Saccone[4] review (1779/5698 participants). Our analysis also demonstrated that the trustworthy studies within Care and Saccone's meta-analyses generated a far more conservative estimate of treatment effects compared to the untrustworthy studies. Therefore, through this review we have demonstrated that a substantial number of RCTs included in meta-analysis published in Cochrane and BMJ are not trustworthy. We have raised our concerns in a letter to the BMJ and are currently awaiting their response.

Whether the lack of trustworthiness is driven by a lack of clear reporting or application methods or by straight fraud is of less relevance, the main priority is that these papers should not be used to inform clinical

practice46. To date, Care et al. since its publication has been cited 54 times3, while Saccone has been cited 239 times4. We believe that this is of significance as the risk of neonatal mortality and morbidity associated with preterm birth is directly affected by current management guidelines and these trials are clearly still being cited, despite clear untrustworthiness.

Discussion

We assessed the trustworthiness of RCTs underlying two meta-analyses published in BMJ. We found trustworthiness concerns in 12/61 studies (2721/17273 participants) in the review of Care et al. and 3/6 studies in the Saccone review (1779/5698 participants). A large RCT from Nooh et al (1272 participants), was published after 2016, and has since been included and later excluded from Cochrane reviews45. Trustworthy studies generated a far more conservative estimate of treatment effects than the untrustworthy studies. Care et al. has since its publication been cited 54 times1, while Saccone has been cited 239 times2.

Our review demonstrates that a substantial number of RCTs included in meta-analysis published in Cochrane and BMJ are not trustworthy. Whether the lack of trustworthiness is driven by a lack of clear reporting or application methods or by straight fraud is of less relevance. Main priority is that these papers should not be used to inform clinical practice.46

We leave what should happen next with the BMJ editors. For progesterone in the prevention of preterm birth, and individual participant data meta-analysis has been done, in which 30 of 47 studies shared data. This meta-analysis with raw data resulted in an even more conservative estimate of the treatment effect of progestagnes (vaginal progesterone RR 0·78, 95% CI 0·68-0·90, 17-hydroxyprogesterone caproate (RR 0·83, 95% CI 0·68-

1·01). For antenatal steroids, three authors have indicated that they are willing to share data47. (Stuchtfield, Porto, Gyamfi-Bannerman).

Table 1 - *Overview of Concerning Parameters for Care et. al.[1] Meta-analysis (based on the TRACT checklist)*

Author	Overview of Concerning Parameters for Excluded Trials (based on the TRACT checklist)									
Care et. al.[1]	Registration/Governance	Funding	Author Group	Timeframe	Drop out Rate	Baseline Characteristics	Plausibility of Intervention Usage	IPD Shared with EPPPIC	In Cochrane Database	Cited in Cochrane Review
Ahuja (2015)	X*	X*	✓	X*	X*	X*	✓	X*	X*	X*
Akbari (2009)	✓	X*	X*	✓	X*	X*	✓	X*	✓	✓
Ashoush (2017)	X*	✓	✓	✓	✓	✓	✓	X*	✓	✓
Cetingoz (2011	✓	X*	✓	✓	✓	✓	✓	✓	✓	✓

)										
El-Gharib (2013)	✗*	✗*	✓	✓	✗*	✓	✓	✗*	✓	✓
Ibrahim (2010)	✗*	✗*	✗*	✓	✗*	✗*	✓	✗*	✓	✓
Jabeen (2012)	✗*	✗*	✓	✗*	✗*	✗*	✓	✗*	✓	✗*
Karbasian (2016)	✗*	✓	✓	✓	✓	✓	✓	✗*	✓	✓
Maher (2013) **RETRACTED**	✗*	✓	✗*	✗*	✓	✓	✓	✗*	✓	✓
Pirijani (2017	✓	✗*	✓	✓	✓	✓	✓	✗*	✓	✗*

)										
Saghafi (2011)	✗*	✗*	✓	✓	✗*	✓	✓	✗*	✓	✓
Wajid (2016)	✗*	✗*	✗*	✗*	✗*	✗*	✓	✗*	✗*	✗*

✗ - parameter of major concern, ✓ - parameter of no concerns*

Table 2 - *Overview of Concerning Parameters for Saccone, Berghella[2] Meta-analysis Excluded Trials (based on the TRACT checklist)*

Author	**Overview of Concerning Parameters for Excluded Trials (based on the TRACT checklist)**						
Saccone, Berghella[2] Meta-analysis	Registration /Governance	Funding	Author Group	Timeframe	Dropout Rate	Baseline Characteristics	Plausibility of Intervention Usage
Ahmed (2015)	✓	✗*	✗*	✗*	✗*	✓	✓

EXPR CONC.							
Balci (2010)	✓	✗*	✓	✗*	✗*	✓	✓
Nada (2016) **RETRACTED**	✗*	✗*	✗*	✓	✓	✓	✓

✗ - parameter of major concern, ✓ - parameter of no concerns*

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