Effectiveness of antenatal corticosteroids at term

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Effectiveness of antenatal corticosteroids at term: can we trust the data that 'inform' us?

--Manuscript Draft--

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Abstract:	Randomized controlled trials (RCTs) are a cornerstone for the assessment of the effectiveness of interventions. Appropriate randomization, design and conduct that reduces the risk of bias and appropriate sample size and statistical analyses enhance the chance they will deliver true research findings. The credibility of RCTs is difficult to assess without objective evidence of complicance with Good Clinical Practice standards. Remarkably no mechanisms are in place both in the initial peer review process and during meta-analysis to assess these, and little guidance on how to assess data where research integrity cannot be confirmed (e.g. where data originated from a setting without establised infractructure or from an era preceding current standards). We describe the case of use of antenatal steroids. When these drugs are used in early preterm birth, there benefits outweigh the harms. However, later in pregnancy, and specifically at term this balance is less clear. We describe that for the four randomised clinical trials that inform clinical practice through the Cochrane meta-analysis, for various reasons, lack of clear governance which make it difficult to verify provenance and reliability of the data. We conclude that transparency and assessment of data credibility needs to be inbuilt both at the time of publication, and at the time of meta-anlaysis. This will drive up standards and encourage appropriate interpretation of results and the context from which they were derived.

Professor Janesh Gupta, MSc, MD, FRCOG
Editor-in-Chief
European Journal of Obstetrics & Gynecology and Reproductive Biology

14th April 2021

Dear Editors of The European Journal of Obstetrics & Gynecology and Reproductive Biology,

Thank you for reviewing our manuscript EJOGRB-21-23676 entitled: *"Effectiveness of antenatal corticosteroids at term: can we trust the data that 'inform' us?"*, that we have submitted for publication to your journal. We have read the comments of the reviewer and adjusted the manuscript accordingly.

Please find an adjusted draft of the manuscript attached. We have marked out the adjustments that have been made in the revised manuscript.

Our reply to the comments of the reviewer is summarised below.

Reviewer #1

The reviewer asks for correction of some minor typing errors.
We have corrected these errors as highlighted in the manuscript, and noted below.

Page 2, Line 6 – 'compliance'
Page 2, Line 10 – 'established infrastructure'
Page 2, Line 12 – 'their'
Page 2, Line 17 – 'meta-analysis'
Page 3, Line 3 – 'distress'
Page 4, Line 16 – 'explanation'
Page 4, Line 24 – 'similar'
Page 5, Line 24 – 'caesarean'
Page 6, Line 9 – 'meta-analysis'
Page 7, Line 3 – 'outweigh'
Page 7, Line 4 – 'prescribed'

We look forward to your response, and thank you for your ongoing consideration.

Yours sincerely,

Table 1: Comparison between the four rrials

	Stutchfield 2005[1]	Ahmed 2015[2]	Nada 2016[3]	Nooh 2018[4]
Titles	Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial.	Antenatal steroids at 37 weeks, does it reduce neonatal respiratory morbidity? A randomized trial.	Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial.	Does implementing a regime of dexamethasone before planned CS at term reduce admission with respiratory morbidity to NICU? An RCT.
Authors	Stutchfield P, Whitaker R, Russell I	Ahmed MR, Ahmed WAS, Mohammed TY	Nada AM, Shafeek MM, El Maraghy MA, Nageeb AH, Salah El Din AS, Awad MH	Nooh AM, Abdeldayem HM, Arafa E, Shazly SA, Elsayed H, Mokhtar WA
Corresponding Author	Stutchfield P	Ahmed MR	Nada AM	Nooh AM
Affiliations	Conwy and Denbighshire NHS Trust	Suez Canal University, Egypt	Ain Shams University, Cairo, Egypt	Zagazig University, Egypt
Journal	BMJ	Journal of Maternal-Fetal & Neonatal Medicine	European Journal of Obstetrics & Gynaecology	Journal of Maternal-Fetal & Neonatal Medicine
Publication Year	2005	2015	2016	2018
Dates Of Recruitment	Single center February ‘95 - November 1998. Multi center November ‘98- April ‘02	July 2012 to December 2013	November 2011 to December 2014	September 2012 to August 2016
Date Received At Journal	Not reported	7 May 2014	3 April 2015	30 November 2016
Date Accepted.	27 June 2005	22 August 2014	29 January 2016	6 February 2017
Citation				
Trial Registration	Not registered*	Not registered	Not registered	Not registered

Research Ethics Committee Approval	North West Multi-centre Research Ethics Committee	Suez Canal University	Ain Shams University on 1 November 2011	Zagazig University Hospital
Funding	Wales Office of Research and Development in health and social care (WORD); Conwy and Denbighshire NHS Trust.	Not mentioned	Not mentioned	None
Participants	998	452	1290	1272
Start Recruitment	Feb 1995	July 2012	Nov 2011	Sep 2012
End Recruitment	Dec 2002	Dec 2013	Dec 2014	Aug 2016
No Of Trial Arms	2	2	2	2
Arm 1 (N)	Two intramuscular doses of 12 mg beta-methasone	two intramuscular doses of 12 mg dexa-methasone	dexamethasone 8 mg every 12 h for 2 days	Three intra- muscular (IM) doses of dexamethasone 8mg, 8h apart,
Arm 2 (N)	Care as usual	Care as usual	Intramuscular saline as placebo	Care as usual
No. Of Centres	10	1	1	1
Hospital of Recruitment	10 hospitals in the UK	Suez Canal University Hospitals, Egypt	Ain Shams University Maternity Hospital	Zagazig University Hospital, Egypt
Method of Randomisation	Random number generator MS Excel; telephone	Not stated	Computer-based tables, and allocation was performed using the closed envelope technique.	Computer-generated randomization sequence using serially numbered, opaque, sealed envelopes
Compliance With Allocated Treatment	26 not given, 7 one dose given, 1 too many doses, 5 not recorded, 8 withdrawn	Not reported	Not reported	Not reported
Lost To Follow-Up	29	0	0	0

*Trial conduct before the introduction of compulsory trial registration policy which requires prospective registration for any clinical trials starting enrolment after 1 July 2005

Supplement to "Effectiveness of antenatal corticosteroids at term: can we trust the data that 'inform' us?"

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INTRODUCTION

This supplement provides further background into our main article regarding the use of antenatal corticosteroids at term, and highlights details on the governance within the trials identified. It contains a description of the methods used to assess trials undertaken by the three of the four lead authors used in the Sotiriadis Cochrane review[1], a detailed overview other studies by these authors, as well as supplementary tables and figures.

METHODS

Inclusion of RCTs

We searched PubMed for RCTs by each of the three first authors of studies identified to have a high risk of bias in the Sotiriadis Cochrane review[1], using the names 'Stutchfield P', 'Ahmed MR', 'Nada AM' and 'Nooh AM'.

Data Extraction

From the articles identified in our search, data regarding year of publication, journal, trial registration number, number of study centres, baseline characteristics, number of participants, outcome data, study start and end dates, and date of submission to the journal was extracted. The average number of randomised participants per month for each study was calculated using the total number of randomised participants and the number of months of recruitment. Additionally, we also searched for trial registration numbers using the World Health Organization (WHO) and International Standard Randomized Controlled Trial Number (ISRCTN) registers.

Comparison of Baseline Characteristics and Outcomes

Our study makes pairwise comparisons of entries in the tables presenting summaries of baseline characteristics and outcome measures to look for identical or similar values across RCTs. Where available, we compared values of mean, standard deviation (SD), percentage, t-value, p-value, and confidence intervals (CIs).

Trial Registration

Where a trial registration number was identified, the status of each study's trial registration was rated based on timing of registration and start of recruitment as either adequate (prior to commencing recruitment or within 6 months of initiating recruitment), or inadequate. An inadequate trial registration status was further categorised as either: late (after 6 months of initiating recruitment but before the completion of recruitment), retrospective (trials registered after completing recruitment) or absent (not registered).

Probability of Random Sampling of Baseline Characteristics

Using Monte Carlo simulations (1), baseline characteristics given as continuous variables were used to generate p-values to describe differences between the intervention and control group of RCTs by each author. When randomization and data recording are performed corrected in the majority of the RCTs, the set of simulation-generated p-values from baseline variables should be approximated by a uniform [0,1] distribution. However, if the generated p-values are over-represented at either 0 or 1 when compared to values in the middle of the uniform distribution on [0,1], this demonstrates systematic baseline imbalance or extreme similarity; and indicates that the group allocation was inconsistent with randomisation. Kolmogrov-Smirnov (KS) tests were further used to compare the distribution for the simulation-generated p-values of baseline variables against the reference of a uniform [0,1] distribution. A smaller p-value generated from the KS test indicates a lower likelihood that the data sourced from the RCTs was adequately randomised. The statistical analyses were performed using Stata (v16.0) and the R statistical software (v3.5.1).

RESULTS

Our search identified eight RCTs authored or co-authored by Ahmed, eight RCTs authored or co-authored by Nada, and three RCT articles authored by Nooh (Tables 1, 3 and 5). For Stutchfield we did not find other RCTs.

Ahmed Studies

The Ahmed articles date from May 2014 to February 2019 and included 1,713 participants in total. The median number of trial participants per study was 203 (range 78 to 452), and the median number of recruitments per month was 14 (range 6 to 25). No trial registration numbers were found for any of the articles. (Table 2)

Study Details

“Aref 2019” is an RCT that evaluates co-administration of aspirin in tamoxifen ovulation induction in anovulatory PCOS women. The study does not report on ovulation rate, but instead measures cumulative clinical pregnancy rates after a maximum of three cycles of 37.2% (aspirin) versus 22.3% (control).[2] “Shabaan 2016b” is a single center study randomizing 132 women in 14 months undergoing myomectomy to having tranexamic acid or not.[3] “Ahmed (WA) 2016a” randomizes 74 women to cervical ripening with Cook balloon or Foley catheter.[4] “Ahmed 2014” reports on 3 moments of timing of urinary catheter removal after uncomplicated total abdominal hysterectomy (immediately after surgery, after 6 hours and 24 hours) and finds a remarkable increase of the postoperative hospital stay of more than 2 days if a catheter is removed after 24 hours in stead of after 6 hours.[5]

Dr Ahmed published four RCTs on women undergoing caesarean section. Apart from “Ahmed 2015a” (n=452, Jul-2012 to Dec-2013) - which was included in the Sotiriadis Cochrane review[1,6] -, “Ahmed 2015b” reports on tranexamic acid in decreasing blood loss in elective caesarean delivery (n=124, Apr-2013 to Oct-2013), “Ahmed 2018” reports on a three-arm randomised clinical trial evaluating regimens for bowel recovery (n=300, Jul-2015 to Aug-2016), and “Ahmed 2017” reports on chlorhexidine vaginal wipes prior to elective cesarean section (n=218; Oct-2014 to Dec-2015).[7-9] Whilst the recruitment period of “Ahmed 2015b” is completely within the period covered by “Ahmed 2015a”, the two studies do not mention each other.

Comparison of Baseline Characteristics

The mean BMI in women undergoing CS in “Ahmed 2015b” was 27.57 versus 28.16 in the two groups, while the median BMI in “Ahmed 2015a” in women undergoing CS was 31.1 versus 30.6.[6,7] The mean BMI in “Ahmed 2017” and “Ahmed 2018” at baseline is in the middle of the two previous studies (29.5 ± 2.9 versus 30.1 ± 3.5), but remarkably identical to each other.[8,9] (Figure 1)

The distribution of indication for caesarean section in “Ahmed 2015b” is reported as: previous cesarean section (n=100; 81%), abnormal presentations (n=12; 10%), maternal request (n=9; 8%), previous repair of cystocele and/or complete perineal tear (n=3; 2%).[7] For “Ahmed 2015a”, indications are: previous cesarean section (n=196; 43%), previous hysterotomy/myomectomy (n=82; 18%), abnormal presentations (n=128; 28%), maternal request (n=30; 6.6%), and others (n=16; 3.5%).[6] In “Ahmed 2017”, indications are: previous cesarean section (n=142; 65%), abnormal presentations (n=10; 4.6%), maternal request (n=44; 20.1%), cephalo-pelvic disproportion (n=15; 6.9%), previous classic repair (n=7; 3.2%).[9] Similarly, the indications in Ahmed 2018 are: previous cesarean section (49%), abnormal presentations (15%), maternal request (14%), cephalo-pelvic disproportion (8%), others (14%).[8]

Probability of Random Sampling of Baseline Characteristics

The distribution of Monte Carlo simulation-generated p-values for the Ahmed group of RCTs significantly deviated from the expected uniform distribution with a KS test p-values of 0.01703. This indicates a low likelihood that the continuous baseline characteristics in this groups of articles were generated as a result of appropriate randomisation. (Figure 2)

Nada Studies

The Nada articles date from November 2010 to February 2017 and included 2,031 participants. The median number of trial participants per study was 209.5 (range 70 to 595), and the median number of recruitments per month was 16 (range 10 to 27). Of these trials, two had adequate registration, three had late registration (Nada 2018b, Nada 2016b and Mansour 2011), and four were not registered. (Table 4)

Study Details

"Al-Inany 2010" reports on an RCT comparing human menopausal gonadotrophins (hMG) followed by clomiphene citrate versus hMG alone in women undergoing IUI that shows a reduction of patients with a premature LH surge.[10] "Mansour 2011" reports on an RCT comparing hysterosalpingography (HSG) with a thin catheter versus normal HSG and reports less pain.[11] The paper does not mention trial registration, but an Internet search revealed a similar trial registered by the first and last author (Mansour and Al-Inany NCT01032642) that is registered after completion of the trial but before submission of the article. (Table 4) The study is registered as completed with 70 patients, while the published paper reports on 89 patients.[12] "Maged 2015" reports on an RCT comparing a delayed start versus a conventional GnRH antagonist protocol in poor responders.[13] "Nada 2016a" reports on an RCT comparing antagonist protocol versus clomiphene in IUI in unexplained infertility.[14] "Nada 2016b" evaluates the efficacy of oral versus vaginal misoprostol in cervical priming prior to operative hysteroscopy.[15] "Nada 2016c" – included in the Sotiriadis Cochrane review – assesses the effect of corticosteroid administration prior to elective caesarean section in reducing neonatal respiratory morbidity.[16] "Nada 2018a" investigates whether the use of saline enemas in the first stage of labour reduces the risk of neonatal C. difficile colonisation.[17] "Nada 2018b" compares outcomes of intracytoplasmic sperm injection and embryo transfer with and without laser-assisted hatching in a population of women with endometriosis.[18]

Probability of Random Sampling of Baseline Characteristics

The distribution of Monte Carlo simulation-generated p-values for the Nada RCTs significantly deviated from the expected uniform distribution with a KS test p-values of 0.00395. This indicates a low likelihood that the continuous baseline characteristics in these groups of articles were generated as a result of appropriate randomisation. (Figure 2)

Nooh Studies

The Nooh articles date from April 2016 to March 2018 and included 1,610 participants. The median number of trial participants per study was 192 (range 146 to 1,272), and the median number of recruitments per month was 11 (range 6 to 26). No trial registration numbers were found for any of the articles. (Table 6)

Study Details

‘”Nooh 2018” – part of the Sotiriadis Cochrane review – evaluated whether dexamethasone prior to elective caesarean section reduced admission to neonatal intensive care for respiratory morbidity.[19] “Nooh 2017” compared reverse breech extraction versus pushing the impacted fetal head up through the vagina in caesarean section for obstructed labour; and reported a mean duration of surgery of 64 minutes.[20] “Nooh 2016” reported on 158 women randomised to Depo-Provera versus Norethisterone Acetate in management of endometrial hyperplasia without atypia with 6 months follow-up and including a set of side effects reported in all women.[21]

Probability of Random Sampling of Baseline Characteristics

The Nooh trials had too few baseline characteristics to meaningfully interpret simulation generated p-values.

Reference:

Carlisle JB et al. Calculating the probability of random sampling for continuous variables in submitted or published randomised controlled trials PMID: 26032950 Anaesthesia. 2015 Jul;70(7):848-58.

Supplementary Table 1: The Trials of Dr. Ahmed

Study	Journal	Title
Aref 2019	Journal of Gynecology Obstetrics and Human Reproduction[2]	A new look at low-dose aspirin: Co-administration with tamoxifen in ovulation induction in anovulatory PCOS women
Ahmed 2018	Journal of Perinatal Medicine[8]	Efficacy of three different regimens in recovery of bowel function following elective cesarean section: a randomized trial
Ahmed 2017	The Journal of Maternal-Fetal & Neonatal Medicine[9]	Chlorhexidine vaginal wipes prior to elective cesarean section: does it reduce infectious morbidity? A randomized trial
Shaaban 2016b	Reproductive Sciences[3]	Efficacy of Tranexamic Acid on Myomectomy-Associated Blood Loss in Patients With Multiple Myomas: A Randomized Controlled Clinical Trial
Ahmed (WA) 2016a	Journal of Obstetrics and Gynaecology Research[4]	Use of the Foley catheter versus a double balloon cervical ripening catheter in pre-induction cervical ripening in postdate primigravidae
Ahmed 2015b	The Journal of Maternal-Fetal & Neonatal Medicine[7]	Efficacy of tranexamic acid in decreasing blood loss in elective caesarean delivery
Ahmed 2015a	The Journal of Maternal-Fetal & Neonatal Medicine[6]	Antenatal steroids at 37 weeks, does it reduce neonatal respiratory morbidity? A randomized trial
Ahmed 2014	European Journal of Obstetrics & Gynecology and Reproductive Biology[5]	Timing of urinary catheter removal after uncomplicated total abdominal hysterectomy: a prospective randomized trial

Supplementary Table 2: Characteristics of Trials of Dr. Ahmed

Study	Registration	Date Registered (D-M-Y)	Centres	Recruitment (M-Y)		Total Women Analysed	Months[b]	No. of Inclusions Per Month[c]	Article Submission (M-Y)
				Start[a]	End[a]				
Aref 2019[2]	N/A	N/A	Single Centre Suez Canal University	Mar-2015	Apr-2016	188	14	13	Sep-2018
Ahmed 2018[8]	N/A	N/A	Single Centre Suez Canal University	Jul-2015	Aug-2016	300	14	21	Sep-2017
Ahmed 2017[9]	N/A	N/A	Single Centre Suez Canal University	Oct-2014	Dec-2015	218	15	15	May-2016
Shaaban 2016b[3]	N/A	N/A	Single Centre Suez Canal University	Feb-2014	Apr-2015	132	15	9	Not Found
Ahmed WA 2016a[4]	N/A	N/A	Single Centre Suez Canal University	Mar-2013	Apr-2014	78	14	6	Nov-2015
Ahmed 2015b[7]	N/A	N/A	Single Centre Suez Canal University	Apr-2013	Oct-2013	124	7	18	Apr-2014
Ahmed 2015a[6]	N/A	N/A	Single Centre Suez Canal University	Jul-2012	Dec-2013	452	18	25	May-2014
Ahmed 2014[5]	N/A	N/A	Single Centre Suez Canal University	Apr-2010	Dec-2012	221	33	7	Jul-2013

N/A = Not Applicable

[a] As described in the paper.

[b] Calculated from recruitment start and end date (inclusive)

[c] Calculated by dividing the number of women analysed with the number of months (rounded to nearest whole number)

Supplementary Figure 1: **Similarities Between D. Ahmed 2017 and Dr. Ahmed 2018**[8,9]

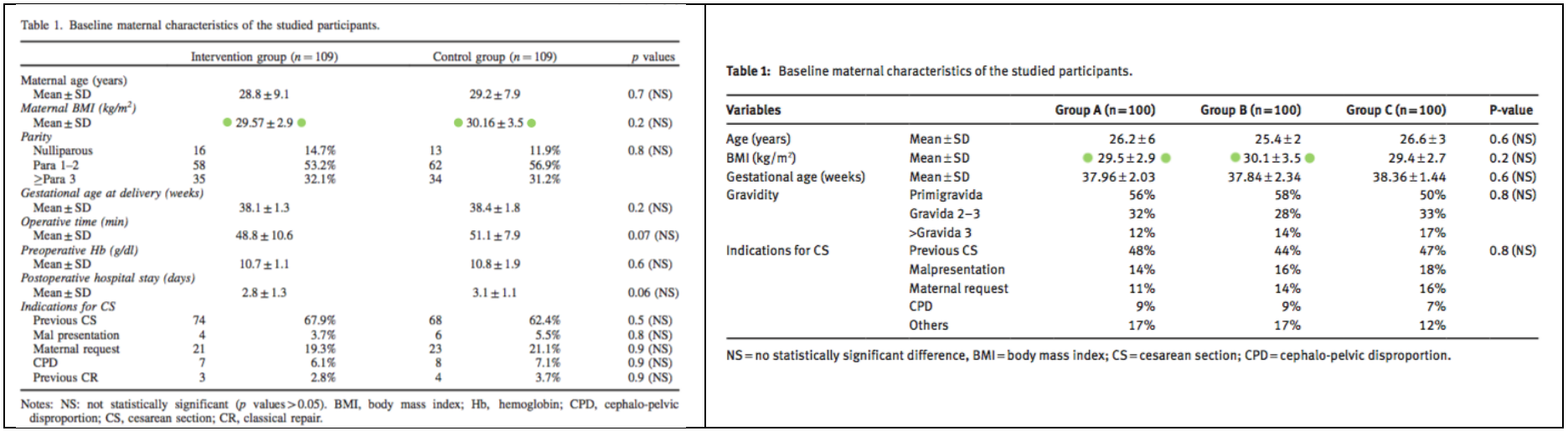


Table 1. Baseline maternal characteristics of the studied participants.

		Intervention group ($n=109$)		Control group ($n=109$)		p values
Maternal age (years)						
Mean ± SD		28.8 ± 9.1		29.2 ± 7.9		0.7 (NS)
Maternal BMI (kg/m²)						
Mean ± SD		29.57 ± 2.9		30.16 ± 3.5		0.2 (NS)
Parity						
Nulliparous	16		14.7%	13	11.9%	0.8 (NS)
Para 1–2	58		53.2%	62	56.9%	
≥Para 3	35		32.1%	34	31.2%	
Gestational age at delivery (weeks)						
Mean ± SD		38.1 ± 1.3		38.4 ± 1.8		0.2 (NS)
Operative time (min)						
Mean ± SD		48.8 ± 10.6		51.1 ± 7.9		0.07 (NS)
Preoperative Hb (g/dl)						
Mean ± SD		10.7 ± 1.1		10.8 ± 1.9		0.6 (NS)
Postoperative hospital stay (days)						
Mean ± SD		2.8 ± 1.3		3.1 ± 1.1		0.06 (NS)
Indications for CS						
Previous CS	74		67.9%	68	62.4%	0.5 (NS)
Mal presentation	4		3.7%	6	5.5%	0.8 (NS)
Maternal request	21		19.3%	23	21.1%	0.9 (NS)
CPD	7		6.1%	8	7.1%	0.9 (NS)
Previous CR	3		2.8%	4	3.7%	0.9 (NS)

Notes: NS: not statistically significant (p values > 0.05). BMI, body mass index; Hb, hemoglobin; CPD, cephalo-pelvic disproportion; CS, cesarean section; CR, classical repair.

Table 1: Baseline maternal characteristics of the studied participants.

Variables		Group A (n=100)	Group B (n=100)	Group C (n=100)	P-value
Age (years)	Mean ± SD	26.2 ± 6	25.4 ± 2	26.6 ± 3	0.6 (NS)
BMI (kg/m²)	Mean ± SD	29.5 ± 2.9	30.1 ± 3.5	29.4 ± 2.7	0.2 (NS)
Gestational age (weeks)	Mean ± SD	37.96 ± 2.03	37.84 ± 2.34	38.36 ± 1.44	0.6 (NS)
Gravidity	Primigravida	56%	58%	50%	0.8 (NS)
	Gravida 2–3	32%	28%	33%	
	>Gravida 3	12%	14%	17%	
Indications for CS	Previous CS	48%	44%	47%	0.8 (NS)
	Malpresentation	14%	16%	18%	
	Maternal request	11%	14%	16%	
	CPD	9%	9%	7%	
	Others	17%	17%	12%	

NS = no statistically significant difference, BMI = body mass index; CS = cesarean section; CPD = cephalo-pelvic disproportion.

"Ahmed 2017" (left; The Journal of Maternal-Fetal & Neonatal Medicine) reports on chlorhexidine vaginal wipes prior to elective cesarean section, whilst "Ahmed 2018" (right; Journal of Perinatal Medicine) reports on a three-arm randomised clinical trial evaluating regimens for bowel recovery following elective caesarean section. The green dots represent exact same values.

Supplementary Table 3: RCTs of Dr. Nada

Study	Journal	Title
Nada 2018b	Archives of Gynaecology and Obstetrics[18]	Effect of laser-assisted zona thinning, during assisted reproduction, on pregnancy outcome in women with endometriosis: randomized controlled trial
Nada 2018a	Journal of Hospital Infection[17]	Does saline enema during the first stage of labour reduce the incidence of Clostridium difficile colonization in neonates? A randomized controlled trial
Nada2016c	European Journal of Obstetrics and Gynaecology[16]	Antenatal corticosteroid administration before elective caesarean section at term to prevent neonatal respiratory morbidity: a randomized controlled trial.
Nada 2016b	Journal of Minimally Invasive Gynecology[15]	Cervical Priming by Vaginal or Oral Misoprostol Before Operative Hysteroscopy: A Double-Blind, Randomized Controlled Trial
Nada 2016a	Taiwanese Journal of Obstetrics & Gynecology[14]	Antagonist protocol versus clomiphene in unexplained infertility: A randomized controlled study
Nada 2015	Reproductive Sciences[13]	Delayed Start Versus Conventional GnRH Antagonist Protocol in Poor Responders Pretreated With Estradiol in Luteal Phase: A Randomized Controlled Trial
Mansour 2011	Postgraduate Medical Journal[11]	A simple and relatively painless technique for hysterosalpingography, using a thin catheter and closing the cervix with the vaginal speculum: a pilot study
Al-Inany 2010	Fertility and Sterility[10]	The effectiveness of clomiphene citrate in LH surge suppression in women undergoing IUI: a randomized controlled trial

Supplementary Table 4: Characteristics of RCTs of Dr. Nada

Study	Registration	Date Registered (D-M-Y)	Centres	Recruitment (M-Y)		Total Women Analysed	Months[b]	No. of Inclusions Per Month[c]	Article Submission (M-Y)
				Start[a]	End[a]				
Nada 2018b[18]	PACTR201602001467322	10-02-2016	Cairo University Hospital, two IVF Centres Cairo & Beni-Suif	Jul-2015	Jan-2017	308	19	16	May-2017
Nada 2018a[17]	N/A	N/A	Cairo University Hospital	Jan-2016	Jul-2016	189	7	27	Dec-2017
Nada 2016c[16]	N/A	N/A	Ain Shams University Maternity Hospital	Nov-2011	Dec-2014	1290	38	34	April-2015
Nada 2016b[15]	PACTR201502001022393	01-02-2015	Department of Obstetrics and Gynecology, Cairo University Hospital	Jan-2014	Jan-2016	390	25	16	May-2016
Nada 2016a[14]	N/A	N/A	Saudi centres Samir Abbass and Assisted Reproductive Techniques Centre of Cairo University,	Jan-2011	Jan-2014	595	37	16	Not Found
Maged 2015[13]	N/A	N/A	4 IVF centres in 2 countries (Egypt and Saudi Arabia)	Jan-2014	Apr-2015	160	16	10	Not Found
Mansour 2011[11]	NCT01032642	15-12-2009	Obstetrics and Gynecology	Mar-2008	Aug-2008	89 [d]	6	15	Jul-2010

			Department at Cairo University						
Al-Inany 2010[10]	ACTRN12607000568415	05-11-2007	Kasr El-Aini Teaching Hospital	Jan-2008	Jul-2009	230	19	12	Sep-2009

N/A = Not Applicable

[a] As described in the paper.

[b] Calculated from recruitment start and end date (inclusive)

[c] Calculated by dividing the number of women analysed with the number of months (rounded to nearest whole number)

[d] Trial registration reports different numbers and a different recruitment period .

Supplementary Table 5: RCTs of Dr. Nooh

Study	Journal	Title
Nooh 2018	The Journal of Maternal-Fetal & Neonatal Medicine[19]	Does implementing a regime of dexamethasone before planned cesarean section at term reduce admission with respiratory morbidity to neonatal intensive care unit? A randomized controlled trial
Nooh 2017	Journal of Obstetrics and Gynaecology[20]	Reverse breech extraction versus the standard approach of pushing the impacted fetal head up through the vagina in caesarean section for obstructed labour: A randomised controlled trial
Nooh 2016	Reproductive Sciences[21]	Depo-Provera Versus Norethisterone Acetate in Management of Endometrial Hyperplasia Without Atypia

Supplementary Table 6: Characteristics of RCTs of Dr. Nooh

Study	Registration	Date Registered (D-M-Y)	Recruitment (M-Y)		Total Women Analysed	Months[b]	No. of Inclusions Per Month[c]	Article Submission (M-Y)
			Start[a]	End[a]				
Nooh 2018[19]	N/A	N/A	Sep-2012	Aug-2016	1272	48	26	Nov-2016
Nooh 2017[20]	N/A	N/A	Jun-2012	Nov-2013	192	18	11	Nov-2015
Nooh 2016[21]	N/A	N/A	Feb-2013	Jan-2015	146	24	6	Not Found

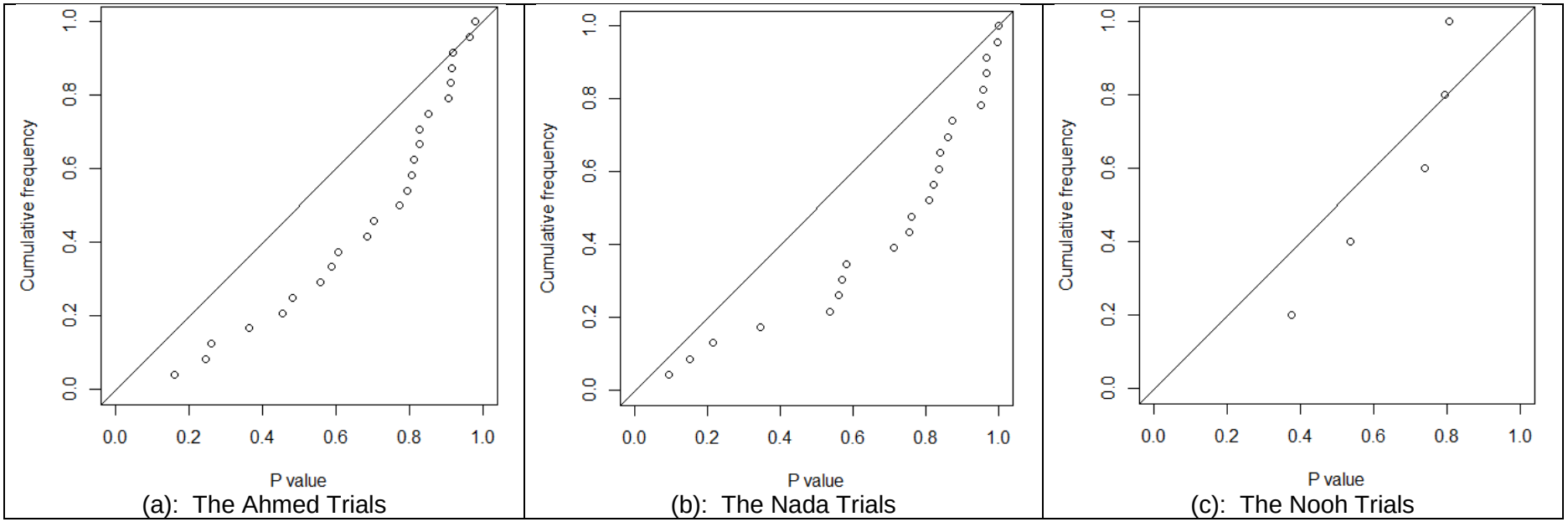
N/A = Not Applicable

[a] As described in the paper.

[b] Calculated from recruitment start and end date (inclusive)

[c] Calculated by dividing the number of women analysed with the number of months (rounded to nearest whole number

Supplementary Figure 2: Cumulative Distribution of Monte Carlo Simulation-Generated p-values for Baseline Characteristics



(a): The Ahmed Trials (b): The Nada Trials (c): The Nooh Trials

The null hypothesis is that the baseline characteristics in intervention and controls groups in these RCTs are the results of a properly conducted randomization process. The distribution was inconsistent with the null hypothesis for both Dr. Ahmed (p=0.01703) and Dr. Nada (p=0.00395) trials suggesting these baseline characteristics are unlikely to be the results of proper randomization. The trials of Dr. Nooh had too few baseline characteristics to adequately compute.

References

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Effectiveness of antenatal corticosteroids at term: can we trust the data that 'inform' us?

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Abstract

Randomized controlled trials (RCTs) are a cornerstone for the assessment of the effectiveness of interventions. Appropriate randomization, design and conduct that reduces the risk of bias and appropriate sample size and statistical analyses enhance the chance they will deliver true research findings.

The credibility of RCTs is difficult to assess without objective evidence of ~~complicance~~compliance with Good Clinical Practice standards. Remarkably no mechanisms are in place both in the initial peer review process and during meta-analysis to assess these, and little guidance on how to assess data where research integrity cannot be confirmed (e.g. where data originated from a setting without ~~established~~established ~~infractructure~~infrastructure or ~~from~~ an era preceding current standards).

We describe the case of the use of antenatal steroids. When these drugs are used in early preterm birth, ~~there~~ their benefits outweigh the harms. However, later in pregnancy, and specifically at term, this balance is less clear. We describe that for the four randomised clinical trials that inform clinical practice through the Cochrane meta-analysis, for various reasons, lack of clear governance which makes it difficult to verify provenance and reliability of the data. We conclude that transparency and assessment of data credibility need~~s~~ to be inbuilt both at the time of publication, and at the time of meta-~~anlaysis~~analysis. This will drive up standards and encourage appropriate interpretation of results and the context from which they were derived.

Keywords: antenatal corticosteroids, data integrity

Main text

Antenatal corticosteroid treatment is given to pregnant women with imminent delivery when babies are at risk for respiratory ~~ditress~~distress. Recently, a population-based cohort study reported that exposure to maternal antenatal corticosteroid treatment is associated with mental and behavioural disorders in children.[1] In term-born children the difference was 9% vs 6%, and an analysis limited to siblings discordant for treatment exposure confirmed these findings. This adds to something we already knew: antenatal corticosteroids are good for the baby's lungs, but not for the baby's brain.[2]

In view of these findings, it is of the utmost importance to know which baby's lungs benefit from antenatal steroids and which baby's do not. Prior to anticipated preterm delivery, there is benefit to timely antenatal corticosteroid administration. A Cochrane review summarizes the findings of 30 RCTs (7,774 women and 8,158 infants): antenatal steroids improve almost all perinatal outcomes, including perinatal death (RR 0.72, 95% confidence interval (CI) 0.58 to 0.89) and respiratory distress syndrome (RR 0.66, 95% CI 0.56 to 0.77).[3]

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Perhaps as a result of these encouraging results, the use of antenatal steroids prior to elective caesarean section is increasingly common. In Australia, almost 10% of pregnant women receive antenatal corticosteroids and advice on pre-Caesarean steroids is becoming inte~~r~~grated into regional and national guidelines.[9] Given that in infants from women delivering at term the baseline risk of respiratory distress syndrome is low, the risk of neonatal mortality tiny, and

there is compelling evidence of detrimental neurological effects of steroids, it is imperative that the data we rely on must be strong enough to ensure that this is doing more good than harm.

In the Cochrane Review on antenatal corticosteroids for elective Caesarean Section the authors assess the risk of bias of the included data, according to the format of Cochrane. The authors raise some concerns, as only one of the trials is placebo controlled, with high risk of detection and/or performance bias in three of the four studies. There was also high or unclear risk of reporting bias in all studies. A closer look at the risk of bias table in the Cochrane review indicates other significant issues about the data that are included. Two trials were not registered with a recognised trial registry according to Cochrane (although we cannot confirm prospective registration for any of the four trials). In Ahmed et al., the Cochrane review remarks that "in view of the fact that participants were not stratified at trial entry it is unusual that there is 50% in both groups in the gestations of 39 - 39 + 6 in both. "[6] It is not the routine of Cochrane procedures to question the integrity of the data, but these observations indicate concerns.

Some other anomalies in the data that are not described in the Cochrane review are also worthy of further ~~explaination~~explanation. In Nada's study the total cohort ratio of male to female infants is 40.4 to 59.6%. Stutchfield et al. was published by BMJ (IF 30.2) more than 3 years after completion of recruitment. The other papers were submitted within 3-4 months of completion in journals with impact factors of 1.7 and 1.8, respectively.

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Neither the journal editors nor the Cochrane reviewers report whether they assessed if RCTs on antenatal corticosteroids prior to Caesarean Section at term ever took place as described.

None of the publications provide evidence of~~-~~ compliance with current Good Clinical Practice (GCP) standards or any other guidelines. It is important to realise that ~~adherance~~ adherence to these standards requires considerable resources and infrastructure, not readily available in all settings. Three of the four trials are single centre trials in a low-middle income setting. The trial of Stutchfield commenced in 1996, when clinical trial standards were different. None of the trials were prospectively registered. No trial protocols or participant facing materials have been made available.

How then can we reassure ourselves of the rigour of the findings to inform modern obstetric practice? In the context of individual participant data meta-analysis on the use of antenatal corticosteroids and for this study, we have approached the authors, co-authors, their institutes and other local contacts (between August 2019 and September 2020) but nobody as yet has been able to supply the original data, or any trial related documentation. However, funding is not available to support data provision, or navigate governance requirements. The responsibility, and cost incurred, to provide data thus falls on individual researchers, and not on institutions or publishing journals. The study from Ain Shams University published by Nada is part of a Medical Doctorate thesis of the second author, ~~that~~ which was completed in 2014. The data presented in the thesis are the same as in the published paper, but the end of the study is reported to be August 2013 in the thesis versus December 2014 reported in the published paper. This means that 1290 women have been randomised within 2 years in the context of a thesis without additional funding. Interestingly, there is another randomised clinical trial from Ain Shams University that between March 2010 to March 2011 randomised 600 women scheduled for elective ~~cesarean~~ caesarean section at term to dexamethasone 12 mg twice or no intervention.[10] It is remarkable that this study from the same institute, with completely different authors, is not referred to by Nada, as it is remarkable that while the first study shows that antenatal dexamethasone is effective in reducing neonatal respiratory morbidity and admission to NICU, a new placebo controlled randomised trial starts 6 months later in the same center.

The question of data integrity is loaded and complex. We cannot ignore potentially valuable observations because the clinical trial does not adhere to ~~standards that are unattainable~~unattainable standards – either due to the setting or epoch that a trial was performed in. On the other hand, clinicians and patients around the world need assurance of data provenance, and that these data are reliable. Transparency and some assessment of data credibility need~~s~~ to be inbuilt both at the time of publication, and at the time of meta-~~anlaysis~~analysis – to help drive up standards and encourage appropriate interpretation of results and the context from which they were derived.

The edifice of knowledge in medicine has been questioned previously.[11] We have recently reported serious integrity problems in a large number of RCTs.[12 13] Our analysis of 45 RCTs from one institute showed replication of baseline and outcome tables from work of the authors themselves and from other authors, which makes it unlikely that at least a substantial amount of these studies ever took place. While one article was retracted 10 years ago as a result "as it duplicates parts of a paper that had already appeared" - a euphemism for the fabrication of an RCT that took place -, that retraction was never followed by a systematic assessment of the other RCTs of this author.[14] After we earlier in 2020 reported the integrity problems with the 45 RCTs to editors and publishers who had published them, this has until now lead to retraction of 4 RCTs, with only a few editors and publishers notifying us that they are working on the problem.[15-18] Cochrane has decided not to use one other study for meta-analysis, pending clarification about the integrity of the study data, while the other 40 continue to 'inform' clinical practice. [19 20] Similar patterns are seen in other areas of medicine. An analysis of 40 papers from Schietroma indicated that data integrity was seriously compromised, but despite the fact that all involved journals have been informed, only four papers have been retracted.[21]

Antenatal corticosteroids may harm the fetal brain, with long term consequences. In women at high risk for early preterm delivery they reduce neonatal mortality and severe morbidity, and therefore their benefits ~~outweight~~outweigh ~~harms . -~~harms. In women undergoing elective

Caesarean section, these drugs are massively ~~presscribed~~prescribed, partly driven by a Cochrane review that reported a promising statistically significant reduction in RDS while the integrity of these data cannot be verified. Based on our analysis of the literature, we suggest ~~to reconsider~~reconsidering that policy.

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None of the publications provide evidence of compliance with current Good Clinical Practice (GCP) standards or any other guidelines. It is important to realise that adherence to these standards requires considerable resources and infrastructure, not readily available in all settings. Three of the four trials are single centre trials in a low-middle income setting. The trial of Stutchfield commenced in 1996, when clinical trial standards were different. None of the trials were prospectively registered. No trial protocols or participant facing materials have been made available.

How then can we reassure ourselves of the rigour of the findings to inform modern obstetric practice? In the context of individual participant data meta-analysis on the use of antenatal corticosteroids and for this study, we have approached the authors, co-authors, their institutes and other local contacts (between August 2019 and September 2020) but nobody as yet has been able to supply the original data, or any trial related documentation. However, funding is not available to support data provision, or navigate governance requirements. The responsibility, and cost incurred, to provide data thus falls on individual researchers, and not on institutions or publishing journals. The study from Ain Shams University published by Nada is part of a Medical Doctorate thesis of the second author, which was completed in 2014. The data presented in the thesis are the same as in the published paper, but the end of the study is reported to be August 2013 in the thesis versus December 2014 reported in the published paper. This means that 1290 women have been randomised within 2 years in the context of a thesis without additional funding. Interestingly, there is another randomised clinical trial from Ain Shams University that between March 2010 to March 2011 randomised 600 women scheduled for elective caesarean section at term to dexamethasone 12 mg twice or no intervention.[10] It is remarkable that this study from the same institute, with completely different authors, is not referred to by Nada, as it is remarkable that while the first study shows that antenatal dexamethasone is effective in reducing neonatal respiratory morbidity and admission to NICU, a new placebo controlled randomised trial starts 6 months later in the same center.

The question of data integrity is loaded and complex. We cannot ignore potentially valuable observations because the clinical trial does not adhere to unattainable standards – either due to the setting or epoch that a trial was performed in. On the other hand, clinicians and patients around the world need assurance of data provenance, and that these data are reliable. Transparency and some assessment of data credibility need to be inbuilt both at the time of publication, and at the time of meta-analysis – to help drive up standards and encourage appropriate interpretation of results and the context from which they were derived.

The edifice of knowledge in medicine has been questioned previously.[11] We have recently reported serious integrity problems in a large number of RCTs.[12 13] Our analysis of 45 RCTs from one institute showed replication of baseline and outcome tables from work of the authors themselves and from other authors, which makes it unlikely that at least a substantial amount of these studies ever took place. While one article was retracted 10 years ago as a result "as it duplicates parts of a paper that had already appeared" - a euphemism for the fabrication of an RCT that took place -, that retraction was never followed by a systematic assessment of the other RCTs of this author.[14] After we earlier in 2020 reported the integrity problems with the 45 RCTs to editors and publishers who had published them, this has until now lead to retraction of 4 RCTs, with only a few editors and publishers notifying us that they are working on the problem.[15-18] Cochrane has decided not to use one other study for meta-analysis, pending clarification about the integrity of the study data, while the other 40 continue to 'inform' clinical practice. [19 20] Similar patterns are seen in other areas of medicine. An analysis of 40 papers from Schietroma indicated that data integrity was seriously compromised, but despite the fact that all involved journals have been informed, only four papers have been retracted.[21]

Antenatal corticosteroids may harm the fetal brain, with long term consequences. In women at high risk for early preterm delivery they reduce neonatal mortality and severe morbidity, and therefore their benefits outweigh harms. In women undergoing elective Caesarean section, these drugs are massively prescribed, partly driven by a Cochrane review that reported a

promising statistically significant reduction in RDS while the integrity of these data cannot be verified. Based on our analysis of the literature, we suggest reconsidering that policy.

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