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Overview of randomised trials of diuretics in pregnancy

RORY COLLINS,   SALIM YUSUF,   RICHARD PETO

Abstract

Over the past 20 years at least 11 randomised trials of the prevention with diuretics of pre-eclampsia and its sequelae have been undertaken. Nine of these were reviewed. Reliable data from the remaining two were not available. The nine reviewed had investigated a total of nearly 7000 people. Significant evidence of prevention of "pre-eclampsia" was overwhelming, even when oedema was not included as a diagnostic criterion. But as the definitions of pre-eclampsia that had been used depended heavily on increases in blood pressure this evidence may simply have reflected the well known ability of diuretics to reduce blood pressure. When the data on perinatal death were reviewed a little difference was seen in postnatal survival. The incidence of stillbirths was reduced by about one third with treatment, but, perhaps owing to small numbers (only 37 stillbirths), the difference was not significant. Thus these randomised trials failed to provide reliable evidence of either the presence or the absence of any worthwhile effects of treatment with diuretics on perinatal mortality.

The implications of this for current and future trials of β blockers and other agents in the prevention of pre-eclampsia and its sequelae are that extremely large, ultra simple randomised trials are needed, of a size sufficient to permit direct assessment of the effects of treatment not on pre-eclampsia but on perinatal mortality itself. This may require the study of tens of thousands of pregnancies.

Clinical Trial Service Unit, Radcliffe Infirmary, Oxford OX2 6HE, and Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford

RORY COLLINS, MB, MSC, medical registrar
SALIM YUSUF, MRCP, DPHIL, medical registrar
RICHARD PETO, MSC, reader in cancer studies

Correspondence to: Dr R Collins, Clinical Trial Service Unit, Radcliffe Infirmary.

Introduction

During pregnancy various physiological abnormalities may be observed in the mother that regress when the pregnancy ends. These include oedema, hypertension, weight gain, hyperuricaemia, proteinuria, activation of coagulation factors, and increased turnover of platelets. Although the mechanisms by which pregnancy can induce such changes remain unclear, when some of these physiological abnormalities become severe— for example, when blood pressure or proteinuria increase rapidly, leading in extreme cases to the development of fits— both mother and child are subjected to an appreciably increased risk. Indeed, even when the changes are relatively moderate they are still associated with a moderate risk of perinatal death. Consequently, the term "pre-eclampsia" has been coined to describe such changes, and several agents have been used in the hope of reducing their degree of severity and consequently avoiding some of the associated perinatal (and maternal) deaths.

From 1960 on, small trials of diuretics and, more recently, other agents have been reported, ranging in size from under 100 up to a few thousand patients. As these studies have been too small to detect realistic effects on mortality they have generally concentrated on the effect of treatment on pre-eclampsia.

Unfortunately, although the term pre-eclampsia is widely used, the underlying mechanisms are so poorly understood that pre-eclampsia has been defined in a bewildering variety of ways, including various combinations of proteinuria, hyperuricaemia, hypertension, and even oedema and weight gain (although oedema and weight gain are not now considered to be of much independent prognostic significance). Of course, if pre-eclampsia is defined partly or wholly by hypertension, by definition any antihypertensive agents such as diuretics, methyldopa, or β blockers must reduce its incidence. This is a matter of definition and not really one that should be addressed by clinical trials. Nevertheless, several trials have reported the ability of antihypertensive agents to reduce the incidence of pre-eclampsia when it was defined partly or wholly by hypertension, as though this question was an open one that needed to be settled by experimentation. Moreover, some trials have been so small that significance was not attained even for these predictable effects of treatment. Only if some treatment was being tested that did not have any known direct effect on the signs used to define pre-eclampsia would it be reasonable to undertake a trial of its effects on the incidence of

pre-eclampsia as a preliminary investigation of its real importance. As, however, the signs of pre-eclampsia and, in particular, hypertension are correlated (though not necessarily directly) with an adverse fetal outcome, most trials have been of agents that are known to affect one or more of those signs. Consequently, the only informative end points in such trials are either signs, such as proteinuria, that are not already known to be affected by treatment or, preferably, as this is ultimately what matters, perinatal mortality. Perinatal mortality is, however, an extremely difficult outcome to study in clinical trials because so few pregnancies result in a stillbirth or neonatal death, and only a proportion even of these are associated with pre-eclampsia.

TABLE I—*Characteristics of randomised controlled trials of diuretics in pregnancy*

| Study | Design | Criteria for entry | Treatment regimen | No followed up | | | No withdrawn | Primary end points | Definition of pre-eclampsia |
				Total	Diuretic treated patients	Control patients			
Zuspan et al[1]	Double blind	Rapid or excessive weight gain. Presence of oedema	Hydrochlorothiazide 100 mg/day × 4 days or 100 mg/day × 2 days plus 50 mg/day × 5 days, or dihydrotrichlorothiazide 10 mg/day × 2 days plus 5 mg/day × 5 days	336	193	143	154	Weight gain	Not used as endpoint
Weseley and Douglas[2]	Double blind	Second or third trimester with ≥2·3 kg weight gain in two weeks or increasing oedema of extremities	Chlorothiazide 100 mg/day until delivery	267	131	136	Nil	Pre-eclampsia Proteinuric pre-eclampsia Stillbirth Neonatal death	CMW*
Flowers et al[3]	Double blind	<30th week. Mean = 19th week	Chlorothiazide 250 mg/day, 500 mg/day, or 750 mg/day until delivery	519 (445)‡	385 (335)‡	134 (110)‡	No details on perinatal deaths for 50 treated patients and 24 controls	Pre-eclampsia Stillbirth Neonatal death	Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg in previously normotensive patient, or appreciable change in hypertensive patient
Menzies[4]	Open control: phenobarbitone	>24th week with systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥85 mm Hg, or ankle oedema, or weight gain ≥1·8 kg in any two weeks after 24th week	Chlorothiazide 100 mg/day plus potassium chloride 2 g/day for a week and continued if indications persist or return	105	57	48	Nil	Pre-eclampsia requiring admission Proteinuric pre-eclampsia Stillbirth Neonatal death	Systolic blood pressure >145 mm Hg or diastolic blood pressure >85 mm Hg or weight gain >0·9 kg in week of treatment; or non-infective albuminuria; or substantial increase in oedema
Fallis et al[5]	Double blind	All primigravid. Expected date of delivery >13 weeks. Diastolic blood pressure <90 mm Hg. Free of oedema and proteinuria	Hydrochlorothiazide 50 mg/day until delivery	78 (74)‡	38 (34)‡	40 (40)‡	Two lost to follow up. No details on perinatal deaths for four treated patients	Pre-eclampsia Stillbirth Neonatal death	CMW*
Cuadros and Tatum[6]	Double blind; "rotational" allocation	≥30 weeks	Bendroflumethiazide 5 mg/day until delivery	1771	1011	760	Nil	Pre-eclampsia Proteinuria Eclampsia Stillbirth Neonatal death	Not available
Landesman et al[7]	Double blind	28th to 32nd week	Chlorthalidone 50 mg/day until delivery	2706	1370	1336	193	Pre-eclampsia Proteinuric pre-eclampsia Stillbirth plus neonatal death	CMW*
Finnerty and Bepko[8]	Open "alternate" allocation	<17 years. No history of renal disease or findings of oedema, increased blood pressure, or albuminuria	Thiazide diuretics until delivery	3083	1340	1743	201 treated patients transferred to control group for "non-compliance"	Pre-eclampsia Stillbirth Neonatal death	Oedema of periorbital area and hands; >10% rise in mean arterial pressure or non-infective albuminuria
Kraus et al[9]	Double blind	<24th week without idiopathic thrombocytopenic purpura, severe diabetes, or sickle cell anaemia	Hydrochlorothiazide 50 mg/day until delivery	1030	506	524	62 treated patients, 47 controls	Blood pressure Pre-eclampsia Stillbirth Neonatal death	CMW*
Tervila and Vartiainen[10]	Single blind	Primigravid >16th week	Chlorthalidone 50 mg/day until delivery	211	108	103	15 treated patients, 19 controls (including two abortions)	Oedema Proteinuric pre-eclampsia Blood pressure Weight gain	Proteinuria ≥0·4 g/d Blood pressure >140/90 mm Hg
Campbell and Mac-Gillivray[11][12]	Open Two controls: 5MJ diet Normal care	Primigravid with weight gain >0·6 kg/week 20th to 30th week	Cyclopenthiazide 0·5 mg/day plus potassium 1·2 g/day, or spironolactone, or clopamide-K	255	153	102	Nil	Pre-eclampsia Proteinuric pre-eclampsia Birth weight	Nelson†

Definitions of pre-eclampsia: *CMW = Committee on Maternal Welfare: increase in systolic blood pressure ≥30 mm Hg or systolic blood pressure ≥140 mm Hg, or increase in diastolic blood pressure ≥15 mm Hg or diastolic blood pressure ≥90 mm Hg, with or without proteinuria or oedema after 24th week.[33] †Nelson: Diastolic blood pressure ≥90 mm Hg after 26th week, with proteinuria (severe) or without (mild).[34]
‡Numbers of patients with follow up for perinatal deaths.
Conversion: *SI to traditional units*—Energy: 1MJ ≈ 240 kcal.

Indeed, unless a group of women at extraordinarily high risk can be identified for study, trials among tens of thousands of women may be needed to pick up the kind of moderate improvements that can realistically be hoped for.

REVIEW OF TRIALS OF DIURETICS

Since 1960 over 10 000 women have been studied in a total of 11 published randomised controlled trials of the use of diuretics in pregnancy (table I).[1-12] It is now generally believed that: (1) the randomised trials have shown that diuretics have no material effect on perinatal mortality[13 14]; (2) the trials that showed some reduction in the incidence of pre-eclampsia[3-9] did so solely because oedema (which is cleared by diuretics) was included in the definitions[13]; and (3) the natural history of progressive pre-eclampsia includes depletion of plasma volume,[13] aggravation of which by diuretics is thought to be potentially hazardous for both mother and fetus.[15 16] We examined to what extent, if at all, the results of the randomised trials supported these beliefs.

In the absence of treatment, the increased perinatal mortality associated with pre-eclampsia is largely confined to those women with severe pre-eclampsia as defined, for example, by a diastolic pressure of 110 mm Hg or more, or by proteinuria with a diastolic pressure of 90 mm Hg or more, or by frank eclampsia.[17] In the presence of antihypertensive treatment, however, the incidence of these signs will be altered, and although studies of the effects of antihypertensive treatment on proteinuria or hyperuricaemia would be of some interest, the real need is to assess correctly the effect of treatment on stillbirths and neonatal deaths. Individually, however, the trials of diuretics that have been conducted to date have been far too small to provide reliable estimates of the type of moderate, but still clinically important, effects that could reasonably be expected on these end points. For example, in England and Wales, where the perinatal mortality rate was 11·8/1000 total births in 1981,[18] reliable assessment even of a halving of this perinatal mortality rate might well require the randomisation of about 10 000 women at normal risk or of several thousand women at high risk. In the absence of trials of this size, however, some useful estimates of the likely effects of diuretics on serious but rare end points such as these may still be obtained by combining the information (irrespective of the results) from all the randomised controlled trials, as is done when the results from individual centres are combined in multicentre trials. Such an overview does not, of course, implicitly assume that the selection criteria, treatment regimens, or definitions of outcome are similar in different trials, for they are not: it assumes merely that patients in one randomised trial can be compared unbiasedly with other patients in the same study.

In addition to the general view that diuretics are likely to be ineffective there have been reports of side effects with their use in pregnancy, including hypokalaemia,[9 10 19] diabetogenic like changes in carbohydrate metabolism,[20] and the masking of hyperuricaemia associated with pre-eclampsia.[21] Much less commonly, neonatal thrombocytopenia and jaundice,[22-24] maternal pancreatitis,[25-27] hyponatraemia, and exacerbation of renal insufficiency[28] have been said to have occurred with the thiazides. As, however, the evidence for these side effects is based on highly selected case reports it does not provide any reliable indication of whatever increase in risk may be associated with the use of diuretics in pregnancy.

This study therefore had two aims. Firstly, to determine whether the overall evidence from all the randomised trials of diuretics in pregnancy supports the current belief that such treatment has no beneficial effect on the incidence of serious end points such as proteinuria or, preferably, perinatal deaths. Secondly, to discuss the errors of interpretation and design of the trials of diuretics that need to be avoided in the current trials of other agents if these are to yield reliable information about the likely effects of treatment. They may otherwise yield either unreliable claims of benefit based on the significance of reductions in the incidence of pre-eclampsia (for which, as has been noted, no trials are needed if the agent being used is known to affect one or more of the signs used to define pre-eclampsia) or unreliable claims of no benefit based on the non-significance of the effect of treatment on perinatal mortality in trials that are too small to show reliably the moderate effects that could reasonably be expected.

Method

ACQUISITION OF DATA

We sought all published randomised controlled trials of diuretics in pregnancy by reviewing reference lists in relevant papers, conducting manual and computer (Medline) searches of published articles, and discussing the subject with colleagues and the authors of studies already identified. Supplementary details of design or outcome were requested from the principal investigators in most instances—for example, if some randomised patients had been excluded from the reported analysis or if numbers of stillbirths, neonatal deaths, or occurrences of eclampsia were not reported. As many of the studies, however, were conducted 10 or 20 years ago, complete information on all randomised patients could not be obtained in some studies. In those studies in which several of the randomised patients were subsequently excluded, therefore, the possibility of some bias remained. Such biases appeared likely to be severe, however, only in the study of Finnerty and Bepko, in which about 13% of the patients originally allocated to the treatment group were transferred to the control group for the purposes of analysis owing to their non-compliance and in which the treated patients, but not the controls, were screened for bacteriuria with subsequent exclusion of any patients in whom it was identified.[8] Data that could rectify these biases no longer appear to exist; we therefore excluded this trial from all "pooled" analyses. The study of Zuspan et al was also excluded as details on pre-eclampsia, stillbirths, and neonatal deaths were not provided and are no longer available.[1]

STATISTICAL METHODS

The fundamental idea in our overview of the results of randomised trials was that, for each separate trial, the patients allocated to treatment and those allocated to control should be compared only with each other, and not with patients in any other trial. From this comparison, a numerical measure (O-E, see below) of the difference in outcome between these two groups was calculated. O-E was the number of patients allocated to treatment who were observed to develop a particular unfavourable event minus the number that would have been expected to have done so on the basis of the combined actual experience of the treated and control patients in that trial. If, in a particular trial, treatment did not have a net effect O-E could equally well be positive or negative and would differ only randomly from zero. On the other hand, if, on balance, treatment prevented a proportion of events O-E would tend to be negative. This would obviously be the case in a trial in which all the patients, without exception, received their allocated treatment. It should also be the case even if some patients deviated from their allocation, for most of those allocated to treatment would have undergone treatment and most of the controls would not. (For reasons discussed by Peto et al, section 13,[29] our analyses are based not on the comparison of patients who actually received treatment with patients who did not but rather on the comparison of patients allocated to treatment and patients not.)

COMBINATION OF INFORMATION FROM MANY TRIALS

In any one trial, however, the play of chance might have exaggerated or obscured the tendency of O-E to be negative, especially if the trial was small or treatment had only a moderate effect. If, however, O-E were calculated separately for each trial and these O-E values, one from each trial, finally added up to yield a grand total (GT), these separate tendencies would be likely to reinforce each other, making GT even more likely to be negative. Conversely, if treatment were without any net effect on outcome each value for O-E would differ only randomly from zero and, therefore, so too would their sum, as long as all randomised trial results were used, without any data dependent

exceptions. The variance (VT) of the grand total would, moreover, then simply be the sum of the variances of the separate O-E values, and these are easily calculated by standard formulas. (Formally, consider a trial in which there are n randomised patients, of whom t are allocated to treatment and c are allocated to serve as controls, and in which d patients suffer a particular unfavourable event. If treatment had no effect on outcome O-E (where $E = t\ d/n$) would have zero expectation and variance $E\ c\ (1-d/n)/(n-1)$. The standard error of the grand total would therefore be the square root of this variance. Throughout, tests of significance (and confidence limits, see below) exploit the fact that the more trials were combined in this way, the more the grand total would tend to have an approximately normal distribution. (Thus, for example, if $GT \simeq -1.96\ \sqrt{VT}$, then the two tailed significance level, 2p, would be approximately 0.05.)

Examination of the grand total assumed that all data from all randomised trials were included without any material bias, such as the withdrawal after randomisation of patients at high risk from the treated group or the unavailability of trials that were not published because they were negative. It did not assume, however, that patients in one trial could be compared directly with patients in another (for it was based solely on the comparison of patients receiving treatment in a particular trial with the controls in the same trial), so that differences in criteria for inclusion of patients or in definitions of end points did not materially bias the test of the null hypothesis. Nor did it assume that, if there were any real effects of treatment, these were necessarily the same in the different trials (see appendix).

Results

PRE-ECLAMPSIA

As the most commonly used indicators of pre-eclampsia are, or were, moderate hypertension or oedema, or both, and as diuretics are known to reduce both of these in normal (non-pregnant) subjects by mechanisms that presumably operate fairly similarly in pregnant subjects, it would be remarkable if diuretics did not reduce the incidence of pre-eclampsia. Yet in nearly half[2] [9-12] of the nine trials that table II lists such an effect was not significantly apparent, presumably because of a combination of the effects of inadequate size and the play of chance. When, however, the nine separate O-E values, one for each trial, were added up their grand total (-52.8, with variance 129.0 and, hence, standard error 11.4) was more than four standard errors below zero, which is highly significant. Despite the reductions in risk being definitely (fig 1) greater in some trials than in others, it is not medically plausible that the true effect would have been zero in any of the trials. Hence the contrast between the high degree of significance of the results of this overview and the lack of significance of the results of four of the nine separate trials illustrates how useful a proper overview of many trials can be as long as, like here, it does not implicitly assume that all trials are similar.

To illustrate that this apparent reduction in the risk of developing pre-eclampsia did not just entail clearance of oedema (which is now not generally considered to be of much relevance to pre-
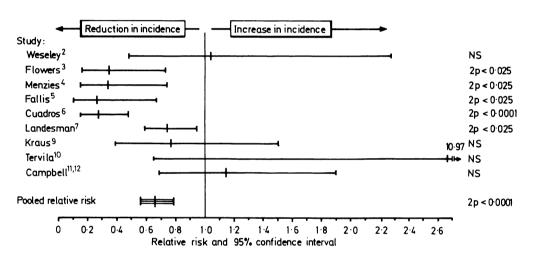

FIG 1—Relative risk of pre-eclampsia (as defined in table I) in individual randomised controlled trials of diuretics, with "pooled" relative risk. Each relative risk is accompanied by approximate 95% confidence limits. Test for heterogeneity: $\chi^2_8 = 29.3$; $2p < 0.001$.

TABLE II—*Results of randomised controlled trials of effects of diuretics on pre-eclampsia*

Study	No of patients followed up		Any form of pre-eclampsia				Severe or proteinuric pre-eclampsia				
	Treated	Control	No in treated patients	No in controls	Treated patients		Definition	No in treated patients	No in controls	Treated patients	
					O-E†	Variance				O-E†	Variance
Weseley and Douglas[2]*	131	136	14	14	+0.3	6.3	Severe pre-eclampsia	3	2	+0.6	1.2
Flowers et al[3]*	385	134	21	17	-7.2	6.8	Not available				
Menzies[4]	57	48	14	24	-6.6	6.1	Non-infective albuminuria	3	5	-1.3	1.9
Fallis et al[5]*	38	40	6	18	-5.7	4.2	Not available				
Cuadros and Tatum[6]	1011	760	12	35	-14.8	11.2	Eclampsia	1	4	-1.9	1.2
Landesman et al[7]*	1370	1336	138	175	-20.5	69.2	Severe pre-eclampsia or eclampsia	20	23	-1.8	10.6
Kraus et al[9]*	506	524	15	20	-2.2	8.5	Not available				
Tervila and Vartiainen[10]*	108	103	6	2	+1.9	1.9	Proteinuria	6	2	+1.9	1.9
Campbell and MacGillivray[11] [12]*	153	102	65	40	+2.0	14.9	Proteinuric pre-eclampsia	19	15	-1.4	7.1
Overall:											
Any form of pre-eclampsia	3759	3183	291 (7.7%)	345 (10.8%)	-52.8	129.0					
Pre-eclampsia, oedema not a diagnostic criterion	2691	2375	265 (9.8%)	286 (12.0%)	-31.4	111.7					
Severe or proteinuric pre-eclampsia	2830	2485						52 (1.8%)	51 (2.1%)	-3.9	23.9

	"Pooled" relative risk	95% confidence interval	Test for heterogeneity
Any form of pre-eclampsia	0.66	0.56, 0.79 (2p < 0.0001)	$\chi^2_8 = 29.3$ (2p < 0.0005)
Pre-eclampsia, oedema not a diagnostic criterion	0.75	0.63, 0.91 (2p < 0.005)	$\chi^2_6 = 15.3$ (2p < 0.025)
Severe or proteinuric pre-eclampsia	0.85	0.57, 1.27 (NS)	$\chi^2_5 = 5.8$ (NS)

*Oedema not a diagnostic criterion.
†The number of patients allocated to treatment who were observed to develop a particular unfavourable event minus the number that would have been expected to do so if treatment had no effect.

eclampsia), those trials in which oedema was not among the diagnostic criteria have been marked with an asterisk in table II, and a separate overview of these confirmed that there was still, as expected, a massively significant effect of treatment. This must, however, be at least in part because of the effects of diuretic treatment on blood pressure. To see whether any effect remained when attention was restricted to criteria, such as proteinuria, that are not as directly affected by diuretics as blood pressure is, the data on more stringent measures of pre-eclampsia were, if available, listed separately to the right in table II. No reliable synthesis of these results is possible, however, because: data from three trials were completely un-available[3] [5] [9]; the available data from three more trials related to pre-eclampsia, albeit of a more severe type, that still depended importantly on blood pressure[2] [7] [11]; and the number of affected patients available for study (103 in all) was inadequate for reliable inference and would have become still more so (only 21 remaining) if end points that depended directly on blood pressure had been ignored.
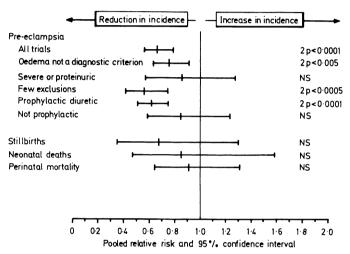

FIG 2—"Pooled" relative risk of pre-eclampsia and perinatal death in randomised controlled trials of diuretics, with approximate 95% confidence limits.

For what they are worth, figure 2 summarises the odds ratios from analyses of various subsets of these data. The real message is, however, clear: in trying to discover what the results of these nine trials implied about the value of diuretics in pregnancy we were forced to concentrate our attention chiefly on perinatal mortality, and the same will be the case when, a few years hence, a sufficient number of trials of β blockers become available for review.

TABLE IV—*Reported side effects in randomised controlled trials of diuretics in pregnancy*

Side effect	Study	Treated patients		Controls	
		No	No with side effect	No	No with side effect
Neonatal					
Thrombocytopenic purpura	Menzies[4]	57	1	48	0
	Kraus et al[9]	506	0	524	0
Jaundice	Flowers et al[3] [24] (Random selection from complete study)	70	13	40	31
Maternal					
Pancreatitis	No cases reported in randomised controlled trials				
Hypokalaemia or hyponatraemia, or both	Flowers et al[3]	No cases in 10% sample and all patients complaining of weakness			
	Menzies[4] Cuadros and Tatum[6] Landesman et al[7] Campbell and MacGillivray[11] [12]	No significant difference in serum sodium or potassium concentrations			
	Kraus et al[9] (Potassium concentration <3·5 mmol(mEq)/l)	506	80	524	37
	Tervila and Vartiainen[10] (Potassium concentration <2·7 mmol/l)	108	4	103	0

PERINATAL MORTALITY

An overview of the data on perinatal mortality (generally considered in these trials to be stillbirths plus neonatal deaths during the first month) suggested a roughly 10% reduction from 1·9% (60/3159) to 1·7% (63/3705), which was not significant despite the randomisation of about 7000 women. (Altogether 2·7 fewer perinatal deaths than expected were observed among patients allocated to receive treatment, while 2·7 more than expected were observed among the controls, suggesting prevention of about five perinatal deaths: formally, the "pooled" relative risk was 0·91, with a 95% confidence interval of 0·64 to 1·31; not significant.) Showing such a moderate reduction in the perinatal mortality rate would, however, be a formidable under-taking (particularly as the perinatal mortality rate is now about 1%[18]) requiring the randomisation of more than 50 000 women.

The data suggested that any real benefit might be concentrated chiefly in the avoidance of stillbirths rather than of neonatal deaths (table III). Although this is merely a hypothesis suggested by the data, and as such is even less reliable than the formal confidence intervals implied, it would be more practicable to test it prospectively. The apparent reduction in the incidence of stillbirths was roughly 30%, but not surprisingly this result was not significant as it was based on only 37 stillbirths in 4000 pregnancies. If diuretics truly reduced stillbirths by 30%, a trial in about 20 000 women might be needed to show such a reduction. Returning to the currently available

TABLE III—*Results of randomised controlled trials of diuretics on perinatal deaths, stillbirths, and neonatal deaths*

Study	No of patients followed up		Perinatal deaths				Stillbirths				Neonatal deaths			
	Treated	Control	No in treated patients	No in controls	Treated patients O-E*	Variance	No in treated patients	No in controls	Treated patients O-E*	Variance	No in treated patients	No in controls	Treated patients O-E*	Variance
Weseley and Douglas[2]	131	136	1	4	−1·5	1·2	1	2	−0·5	0·7	0	2	−1·0	0·5
Flowers et al[3]	335	110	6	3	−0·8	1·6	3	2	−0·8	0·9	3	1	0	0·7
Menzies[4]	57	48	3	2	+0·3	1·2	1	1	−0·1	0·5	2	1	+0·4	0·7
Fallis et al[5]	34	40	1	3	−0·8	1·0	0	1	−0·5	0·3	1	2	−0·4	0·7
Cuadros and Tatum[6]	1011	760	14	13	−1·4	6·5	6	5	−0·3	2·7	8	8	−1·1	3·9
Landesman et al[7]	1370	1336	24	19	+2·2	10·6	Not available				Not available			
Kraus et al[9]	506	524	14	16	−0·7	7·3	6	9	−1·4	3·7	8	7	+0·6	3·7
Tervila and Vartiainen[10]	108	103	0	0	0	0	0	0	0	0	0	0	0	0
Campbell and MacGillivray[11] [12]	153	102	0	0	0	0	0	0	0	0	0	0	0	0
Overall:														
Perinatal deaths	3705	3159	63 (1·7%)	60 (1·9%)	−2·7	29·4								
Stillbirths and neonatal deaths	2335	1823					17 (0·7%)	20 (1·1%)	−3·4	8·8	22 (0·9%)	21 (1·2%)	−1·5	10·3

	"Pooled" relative risk	95% confidence interval	Test for heterogeneity
Perinatal deaths	0·91	0·64, 1·31 (NS)	$\chi^2_8 = 3·5$ (NS)
Stillbirths	0·68	0·35, 1·31 (NS)	$\chi^2_7 = 1·0$ (NS)
Neonatal deaths	0·86	0·47, 1·59 (NS)	$\chi^2_7 = 2·5$ (NS)

*The number of patients allocated to treatment who were observed to develop a particular unfavourable event minus the number that would have been expected to do so if treatment had no effect.

data, however, at least the favourable direction of the results on stillbirth does not support the fears that diuretics may be seriously harmful to the fetus.

SIDE EFFECTS

As various workers have expressed concern, based on inadequately controlled case reports, that diuretics may have adverse effects in pregnancy, particularly by causing neonatal thrombocytopenia and jaundice and maternal pancreatitis, hypokalaemia, and hypo- natraemia,[9 10 19-28] we tabulated the incidence of these side effects in those randomised controlled trials in which they were reported (table IV).[3 4 6 7 9-12 24] There was no significant excess of neonatal thrombocytopenic purpura or jaundice, and no cases of maternal pancreatitis had been reported. Likewise, a significant difference in the incidence of maternal hyponatraemia or hypokalaemia was not reported in most trials, although two trials, which did not use potassium supplementation, did report an increased incidence of hypokalaemia.[9 10] These cases, however, rarely caused any problems. The data suggested that the reported risks of serious side effects of diuretic treatment, which must have contributed to its decreasing popularity, may have been overstated and perhaps have been due, at least in part, to selected case reporting.

Discussion

This overview raises two main questions. Firstly, does such an overview have any real medical relevance or is it merely an empty (or even potentially misleading) statistical exercise? We have discussed above various possible difficulties, and our view is that, as long as the precautions discussed there are adopted, the dangers of attempting such an overview are far less than the dangers of not doing so. Clinical trials often require surprisingly large numbers of participants to show unequivocally even clinically important differences between treated and control patients. The difficulty is increased when the end point is rare (pre-eclampsia, which is severe in only about one fifth of cases, occurs in only about a quarter of pregnancies,[17] and stillbirths, which are thought to be secondary to pre-eclampsia in only about one quarter of cases,[30] occur in less than 1%[18]). The difficulty is increased still further when, as is commonly the case, even a treatment that produces a worthwhile benefit is likely to reduce the incidence of the end point only moderately—for example, by 10, 20, or 30%—rather than by a large amount— for example, by over 50%. When, in these circumstances, trials of inadequate size do not achieve significant results they are often misinterpreted as showing that treatment has no effect (as has occurred in the case of diuretics) when, in fact, the trials are not powerful enough to distinguish between absence of benefit and moderate benefit. Not surprisingly, therefore, a large number of small trials may lead to conflicting results due to the play of chance, whether or not there is really any important heterogeneity of treatment effect.

Secondly, what are the implications for future trials of perinatal treatment with diuretics, β blockers, or other agents? Clearly, from the large number of studies with diuretics performed over 15 years, their inadequate size has resulted in a long controversy. Yet, what practical lessons about the conduct of trials have been learnt from all this? Despite the difficulties in interpreting trials of inadequate size, two recent studies of newer agents (β blockers) in pregnancy randomised only 100 and 120 patients respectively.[31 32] Not surprisingly, they reached opposite conclusions; indeed, one of them actually concluded that there was no significant difference in fetal outcome, although no stillbirths occurred in either treatment group.[31] The lessons of the failure to evaluate diuretics properly must be understood and acted on so that trials of future agents are large enough to be of serious scientific value in assessing the effects of treatment on perinatal mortality. Such trials may, except when patients at peculiarly high risk can be identified, have to include many thousands, perhaps even tens of thousands, of patients. This can be achieved in practice only by extraordinarily

wide collaboration, which in turn probably requires the trial to entail extraordinarily little extra work per patient. If the chief end point is perinatal mortality, whether the effects of treatment on such variables as blood pressure, oedema, or proteinuria—or any other routine clinical observations for that matter—are reported to the trial centre simply does not matter. Depending on the agent or agents being tested, no, or at most very little, extra follow-up or record keeping may be needed over and above ordinary clinical practice. Fortunately, therefore, the conduct of such a trial could be extraordinarily simple, imposing no great burdens on the trial centre or the collaborators in the trial. (The only exception is that, as there are many different modes of perinatal death, only some of which are associated with pre- eclampsia, an effort would have to be made to put the modes of death into subcategories at least to the extent that is rendered possible by retrospective examination of routine records.)

Thus, in trials in which the chief end points are events like perinatal death that are readily assessed from routine records, there is often no need for any appreciable extra work by prospective participants. Unless this fortunate circumstance is exploited to the full, the current and future trials of agents such as β blockers may be as uninformative about perinatal mortality as the trials of diuretics have been. This would be unfortunate, for during the decades while 10 000 patients were being randomised into trials of diuretics, a vast number (perhaps several millions) of pregnant women were treated in an un- controlled way with these agents. In view of the commercial pressures to use β blockers, their unevaluated, uncontrolled use could become at least as widespread as that of diuretics, in which case it might be a prudent, rather than a dis- proportionate, use of resources to randomise some tens of thousands of patients to discover whether β blockers are of any material value. More generally, the same should apply to any other medical treatments that might come into widespread use.

Appendix

If treatment moderately reduced the odds of a particular unfavourable outcome occurring to a roughly similar extent in all trials the grand total and its variance might in addition be used to calculate a "pooled" odds ratio ($POR = exp(GT/VT)$). This is a useful estimate of the ratio of the odds of an unfavour- able outcome among the patients allocated to treatment to that among the controls, with approximate 95% confidence limits ($exp(GT/VT \pm 1.96/\sqrt{VT})$). Because in these trials very few adverse outcomes were observed we have (somewhat loosely) referred to these "pooled" odds ratios as pooled relative risks. The assumption that the true effects in each trial might have been similar, but for the play of chance, can be tested by an approximately "χ^2" test (χ^2 for heterogeneity $\simeq$ the sum, for all k trials with non-zero variance, of $(O-E)^2/V$ minus GT^2/VT, with degrees of freedom $= k-1$). In practice, of course, for important end points (such as perinatal death), it is difficult to obtain enough data to be able to decide reliably whether any net good or harm results from treatment and even more difficult to obtain enough data to estimate reliably the size of any such benefits, even from an overview of many trials. Consequently, the above statistical details can, for most practical purposes, be ignored: what chiefly matters is the simple question of whether there was clear evidence of any net effect of treatment.

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Clinical importance of enteric communication with abdominal abscesses

S H SAVERYMUTTU, A M PETERS, J P LAVENDER

Abstract

The dynamics of leucocytes in abdominal abscesses were studied using indium-111 autologous leucocyte scanning in 30 patients. Thirteen patients showing enteric drainage of leucocytes on delayed scans were characterised by a lack of abdominal localising signs and a low detection rate by ultrasound (25%). By contrast, 16 of 17 patients without enteric drainage had abdominal signs, and in these patients ultrasound was associated with a higher detection rate (58%). Despite the presence of an enteric route of drainage for the abscess 10 of the 13 patients needed surgical intervention.

These results help explain the wide variation in clinical presentation of abdominal abscesses; suggest that ^{111}In leucocyte scanning should be the initial investigation in those patients without focal signs; and show that formal surgical drainage is needed in patients recognised as having enteric communication with abscesses.

Introduction

Despite advances in surgical technique and medical treatment intra-abdominal abscesses remain a common diagnostic problem. Mortality is over 80% in undrained collections[1][2] but may be decreased to less than 30% with effective surgical treatment. The critical factor determining the prognosis of these patients is the difficulty in localising the abscesses. In many abscesses there are classic clinical features with focal abdominal tenderness, and in these cases ultrasound is a rapid, sensitive diagnostic technique.[3][4] In some abscesses, however, the clinical presentation may be insidious with minimal signs of localisation, and these pose much greater problems in diagnosis. This wide range in clinical presentation of intra-abdominal abscesses is unexplained.

During early studies using indium-111 leucocyte scanning we observed that in some abscesses with minimal localising signs there was drainage of labelled leucocytes into the bowel on delayed scans, indicating enteric communication with the abscesses.[5] To investigate whether enteric drainage of pus decompresses the abscess and so accounts for lack of abdominal signs we have examined the incidence of enteric communication with abscesses and related this feature to the clinical presentation.

Royal Postgraduate Medical School, Hammersmith Hospital, London W12
S H SAVERYMUTTU, BSC, MRCP, lecturer in medicine
A M PETERS, MD, senior lecturer in radiology
J P LAVENDER, FRCPED, FRCR, senior lecturer in radiology

Correspondence to: Dr S H Saverymuttu, Medicine II, St George's Hospital Medical School, Tooting, London SW17.

Patients and methods

From August 1981 to December 1983 patients referred to this hospital's department of diagnostic radiology for routine ^{111}In leucocyte scans were included in the study if (*a*) an abscess was detected by the scan, (*b*) the diagnosis was confirmed independently, and (*c*) full clinical details were available for review.

A total of 30 abscesses were studied. Confirmation of the diagnosis