reviews and critiques, and project design, execution, and analysis?
- Do students keep a running portfolio of their assessment performance, with a defined guide on what constitutes satisfactory progress?
- Have all gradings (except satisfactory/unsatisfactory) and all undergraduate prizes, honours, and distinctions been abandoned?

If the answers to these questions are all yes, the forthcoming articles may hold little interest. If not, readers should find the series challenging and valuable in their planning. Evidence-based medicine is the current watchword. Should we not also practise evidence-based assessment?

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Diabetic ketoacidosis

Harold E Lebovitz

With advancing knowledge and newer technologies, the incidence of diabetic ketoacidosis should be falling and morbidity and mortality ought to be small. Yet current data indicate that both premises are incorrect. In the US in 1987, admissions to hospital for diabetic ketoacidosis as a primary diagnosis were 12·5 per 1000 individuals with diabetes (type I and type II), a rate that had risen significantly from 1980.[1] The mortality for these patients was 0·25 per 1000 individuals (2% of those admitted with a primary diagnosis of diabetic ketoacidosis), a rate that had decreased by only 18% from 1980 through 1987. A comparable incidence of diabetic ketoacidosis has been reported recently by the EURODIAB study, which found that 8·6% of 3250 insulin-dependent diabetic patients in Europe had been admitted to hospital for diabetic ketoacidosis one or more times in the previous 12 months.[2]

The mortality rate for ketoacidosis ranges from 2%–5% in developed countries[1,3–5] and 6%–24% in developing countries.[6,7] The most common causes of ketoacidosis are infections (30%), non-compliance with treatment (20%), and newly diagnosed diabetes (25%). About one quarter of cases have no precipitating event. There are no data on the prevalence of diabetic ketoacidosis in non-insulin-dependent diabetic patients but non-caucasian populations with new-onset diabetes or infections present not infrequently with ketoacidosis.

In developed countries, mortality and morbidity from diabetic ketoacidosis result mainly from sepsis or pulmonary and cardiovascular complications,[3–5] especially in individuals over 65 years in whom the mortality rate exceeds 20% compared with about 2% in younger adults.[8] Children and young adults (≤28 years) are uniquely susceptible to the development of severe and often fatal cerebral oedema during the treatment of ketoacidosis.[9–10] This complication is estimated to occur in 0·7%–1·0% of ketoacidotic episodes.[11,12] The goal in management is to re-establish metabolic homoeostasis with minimum morbid events by the most cost-effective measures.

Clinical presentation

Diabetic ketoacidosis can present with hyperglycaemia, ketonaemia, acidosis, dehydration, and hyperosmolarity. There is no consensus definition of what constitutes diabetic ketoacidosis. Blood glucose can vary from less than 11·1 mmol/L (1·1% to 7·6% of cases) to greater than 55·6 mmol/L.[13,14] Arterial pH criteria have been defined by various authorities from as high as <7·35 to as low as <7·20, and plasma bicarbonate from <19 to ≤10 mmol/L.[3–5] Ketonaemia must be present, but is usually

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not precisely measured. Plasma osmolality is increased, but is generally less than 320 mOsm/L, and an increased anion gap (>16 mmol/L) is usual.[3-5] For purposes of uniformity and clarity, the term diabetic ketoacidosis should be confined to those patients with positive serum ketones and an arterial blood pH ≤7·30 and/or a serum bicarbonate ≤15 mmol/L.

The presenting abnormalities in an individual patient are determined by the prodromal events. A lower presenting blood glucose is likely to occur in pregnant women or in those with food deprivation or excessive vomiting with continued insulin administration.[15] A smaller anion gap and greater hyperchloraemic acidosis are found if the individual is able to maintain oral fluid intake and normal renal function.[16] By contrast, dehydration with contracted extracellular fluid volume and reduced renal function increases plasma osmolality and the anion gap acidosis.[16] In developing a treatment strategy, one must assess the status of each of these metabolic abnormalities. Patients with hyperglycaemia, plasma osmolality less than 320 mOsm/L, and arterial blood pH >7·30 can usually be treated adequately as outpatients. Patients with a pH ≤7·20 should be admitted to hospital for intensive management while the treatment scheme for the remainder depends on associated circumstances.[17]

Prevention of complications

Hypoperfusion with thromboembolic disorders

Mortality and morbidity in diabetic ketoacidosis are related to length of time between onset of ketoacidosis and initiation of treatment, presence of sepsis, and age.[3-5,8] Severe dehydration results in decreased perfusion of vital organs and promotes coagulation processes, which can lead to myocardial, bowel, and brain infarctions. Immediate administration of crystalloid or colloid solutions to partly replete decreased extracellular fluid volume is essential but of limited benefit, since many of these complications are present at the time of presentation.[3,4] Major reductions in these complications can be achieved by earlier detection or prevention of ketoacidosis, which should be a key goal of diabetes education programmes.

Cerebral oedema

This complication is the most prevalent and serious threat from diabetic ketoacidosis. Although clinically significant cerebral oedema has occurred in individuals in their twenties, most occurrences have been in children or adolescents. The clinical course is that of a child being treated for diabetic ketoacidosis with good resolution of hyperglycaemia and acidosis. Within 2 h to 24 h of onset of treatment, the individual suddenly develops signs of cerebral oedema (headache, deterioration in level of consciousness).[10-12,18] Neurological deterioration progresses rapidly over several hours with eventual herniation of the brain stem. Cerebral oedema is more likely to occur in previously undiagnosed patients presenting with diabetic ketoacidosis than in those with known diabetes. Occurrence is estimated to be 0·7–1·0 per 100 episodes of ketoacidosis in children. Mortality is about 70% and recovery without permanent impairment of function is only 7% to 14%.

The pathophysiology is poorly understood. Retrospective data analysis suggests that significant risk factors include new-onset diabetes, longer duration of keotacidosis, and exaggerated decreases in serum osmolality during treatment (associated with a failure of serum sodium to rise appropriately).[9-12] Perplexing issues are the unique susceptibility of young individuals and the lack of reported occurrence in the hyperosmolar non-ketotic syndrome where initial chronic hyperosmolarity is substantially greater than that which occurs in ketoacidosis.

Several mechanisms have been proposed to explain the development of cerebral oedema. The hypothesis for which there is the strongest experimental support proposes that the chronic hyperosmolar state of hyperglycaemia generates "idiogenic osmoles" by brain cells to increase osmotic pressure, thereby maintaining their intracellular water content.[12,19,20] These molecules are necessary since glucose that enters the cell is metabolised. With treatment, expansion of the extracellular space with fluids and insulin lower plasma glucose and decrease plasma osmolality. The only compensatory mechanisms available to brain cells are alterations in the intracellular-extracellular cation concentrations. If turnover of "idiogenic osmoles" is slower than the rate at which the extracellular space osmolality is lowered, cerebral oedema would ensue. Increased vasopressin secretion, which is known to occur in diabetic ketoacidosis, would accelerate this imbalance. The accumulation of "idiogenic osmoles" in cerebral cortex has been identified in normal rabbits made hyperglycaemic for 4 h and then normalised rapidly with insulin.[19] Cerebral oedema occurred in those animals when the plasma glucose had fallen to at least 14 mmol/L. In rats with diabetic ketoacidosis, taurine has been shown to be one of these "idiogenic osmoles".[20]

Unfortunately, experiments measuring brain osmoregulation in chronically diabetic animals allowed to go into ketoacidosis and then treated have not been conducted. The hypothesis has not been verified adequately. Other hypotheses include activation of the Na^+/H^+ exchange mechanism in the cerebral plasma membrane through acidification of cytoplasm by weak organic acids, leading to increased sodium accumulation within brain cells[21] and cerebral hypoxia leading to toxic activation of the N-methyl-D-aspartate (NMDA) receptor.[18]

The role of treatment in the development of clinically relevant cerebral oedema has been examined by retrospective case analyses. A rate of fluid administration greater than 4·0 L/m^2 per day had been proposed as a predisposing factor by some investigators[9] and refuted by others.[10] A decrease in serum sodium or a failure of serum sodium to rise as blood glucose falls has been noted in several series;[10,12] it has been suggested that this is a marker for excessive accumulation of free water. An increase in free water is likely to be the result of increased anti-diuretic hormone secretion, together with an excess of intravenously administered free water. These observations have major implications for designing fluid regimen compositions and rates of administration.

Symptom-free or mildly symptomatic cerebral oedema may occur in many children and adults being treated for diabetic ketoacidosis. Subclinical brain swelling was found by computed tomography in a group of six symptomless children treated for diabetic ketoacidosis.[22] Studies in adults with ketoacidosis found increased cerebrospinal fluid pressure[23] or echoencephalogram evidence[24] of cerebral oedema. Some patients developed drowsiness or

Admission

- Diagnosis suspected and confirmed immediately by blood glucose and ketone measurements
- Initial assessment of magnitude of dehydration, hyperosmolarity, and acidosis
- Fluid loss=subtract admission weight from last recently known stable weight
  Effective serum osmolality=2× [serum Na^+ (mmol/L)+serum K^+ (mmol/L)]+serum glucose (mmol/L)]
  Corrected sodium=serum sodium (mmol/L)
  $$+1{\cdot}6\times\frac{\text{Plasma glucose (mmol/L)}-5{\cdot}5}{5{\cdot}5}$$
- Initial assessment of serum potassium and renal function
- Evaluate patient for sepsis and/or precipitating illness.

Hour 1

- *Fluid administration*
  If strikingly hypovolaemic with low blood pressure and relative or absolute anuria: fluid administration should be normal saline and, if necessary, colloids; rate of administration should be that necessary to restore circulatory function.

  When blood pressure is normal and urine output adequate: fluid administration should be normal saline; rate of administration 500–1000 mL/h.
- *Insulin*
  Continuous intravenous infusion of regular insulin 5–10 units/h or intramuscular regular insulin (20 units loading dose and 5 units/h).
- *Potassium*
  Start intravenous potassium at 10–30 mmol/h at initiation of insulin therapy if serum potassium is not >5 mmol/L and renal output is good. If patient is hyperkalaemic, temporarily delay intravenous potassium.
- *Alkali*
  Sodium bicarbonate intravenously is rarely indicated except in severe acidosis (pH<7·0) with incipient circulatory collapse. Dose, if given, is 50–100 mEq sodium bicarbonate given in 0·45% saline over 30–60 min. Additional K^+ must be given with bicarbonate therapy.

Hour 2

- *Fluid administration*
  Continue normal saline at 500 ml/h. Maintain calculated plasma osmolality greater than 285 mOm/L throughout the first 12 h. If serum Na^+>150 mmol/L switch to 0·45% saline.
- *Insulin*
  Check blood glucose and adjust insulin dose to maintain a fall of about 5 mmol/L/h. Do not allow blood glucose to fall below 15 mmol/L. Anion gap should be decreasing and blood pH increasing.
- *Potassium*
  Maintain serum potassium between 4·0–5·0 mEq/L by continued addition of potassium to intravenous fluids.

Hours 3 and 4

Continue as in hour 2.

Observe for cognitive or neurological symptoms and continue to do so for 12 h.

Hours 5 to 8

- *Fluid administration*
  Normal saline 250 ml/h. When blood glucose reaches 15 mmol/L change intravenous fluid to 500 mL/h normal saline with 5% glucose.
- *Insulin*
  Continue insulin at maintenance dose until ketoacidosis has cleared (blood pH>7·35, serum ketones negative).
- *Potassium*
  Continue at 10–30 mEq/h until ketoacidosis has cleared.
- *Phosphate*
  Consider phosphate replacement at 6 h if serum phosphate is less than 2·0 mg/dL..

Hours 8 to 24

- *Fluid administration*
  Continue intravenous repletion with 0·45% saline with or without 2·5% or 5·0% glucose as needed.
- *Insulin*
  After ketoacidosis has cleared (blood pH>7·35, serum ketones negative) switch to subcutaneous insulin and then stop IV or IM insulin.

Table: **Management of diabetic ketoacidosis**

mild neurological symptoms at the time of increased pressure. Cerebral oedema may even exist before therapy.[25,26] The reason for the lack of severe life-threatening cerebral oedema in adults with ketoacidosis is unclear. Studies on cerebral water balance are surprisingly lacking.

Hyperchloraemic acidosis

Hyperchloraemic acidosis results from increased urinary loss of ketones, excessive administration of high-chloride-containing fluids, and intracellular consumption of bicarbonate.[16] Patients who are well hydrated may present with an anion gap and hyperchloraemic acidosis. Most commonly, hyperchloraemic acidosis occurs during intravenous fluid therapy. While some data suggest a slower rate of recovery in patients presenting with or developing hyperchloraemic acidosis, no study shows adverse morbidity or mortality.

Hypokalaemia

Total body potassium is depleted in patients with diabetic ketoacidosis.[4,27] The usual deficit is 3–5 mmol/kg of body weight. Because of shifts between intracellular and extracellular spaces, serum potassium on presentation may be high, normal, or low. Therapy of diabetic ketoacidosis shifts potassium from the extracellular to the intracellular compartment by correction of acidosis, repletion with sodium, and insulin effects on glycogen synthesis and potassium transport into the cell. The continuing renal loss of potassium and the shift of potassium in to the cell can lead to profound hypokalaemia and death if not treated prospectively.

Hypophosphataemia

Diabetic ketoacidosis is associated with severe phosphate depletion (estimated to range from 0·15–1·5 mmol/kg body weight).[27] Serum phosphate concentrations may be high, normal, or low at presentation and these may decrease with treatment because of increased cellular uptake. Though serum concentrations may fall into a range known to be associated with impaired cardiac and skeletal muscle function, respiratory failure, rhabdomyolysis, and decrease in red cell 2,3-diphosphoglycerate concentrations, these complications have been observed only rarely. Several randomised controlled studies of the addition of phosphate to the treatment regimen for diabetic ketoacidosis have not shown any beneficial effects on clinical course or outcome.[28–30] However, these studies have been conducted in individuals without significant cardiopulmonary complications in whom hypophosphataemia might be most deleterious.

Hypoglycaemia

Treatment of diabetic ketoacidosis should avoid significant hypoglycaemia. Treatment regimens with high-dose subcutaneous insulin lead to significantly more early and late hypoglycaemia than low-dose intramuscular or intravenous insulin.[31,32] Permanent cerebral dysfunction can result from prolonged (>4 h) severe hypoglycaemia.

Treatment plan

A reasonable treatment scheme for diabetic ketoacidosis (table) can be formulated based on these data.

Diagnosis

Diagnosis must be made rapidly and treatment initiated early. Difficulty in diagnosis may occur in patients presenting for the first time with diabetic ketoacidosis or in those with acute macrovascular disease, or infections that overshadow the more subtle signs and symptoms of ketoacidosis. The usual qualitative tests for ketones do not detect beta-hydroxybutyrate and, in strikingly reduced states, can give misleading estimates of ketosis. Conversely, drugs such as captopril can give false-positive tests for urinary acetone.[4]

Fluid management

Restoration of extracellular fluid volume by intravenous crystalloids or colloids is critical to maintain adequate cardiac output and renal function. Expansion of the extracellular space in ketoacidosis by intravenous administration of fluids facilitates glucose excretion and decreases secretion of counter-regulatory hormones.[33,34] A significant fall in blood glucose and serum osmolality occur even in the absence of insulin administration. However, no significant improvement occurs in arterial blood pH, serum bicarbonate, or plasma ketone concentrations.

The major questions concerning repletion of the extracellular fluid compartment are first, what should be the osmolality of the administered fluid?; second, how rapidly should fluids be administered?; and third, are colloid solutions to be perferred over crystalloid solutions? Very few controlled studies are available to answer these important questions. It is often presumed that unless there is severe volume depletion, hypotonic solutions should be administered since these individuals are more deficient in free water than in electrolytes. However, intravenous administration of hypo-osmotic fluids rapidly decreases extracellular fluid osmolality and predisposes to free water entry into cells that are still hyperosmolar. As discussed earlier, retrospective analyses of individuals who developed clinically significant cerebral oedema suggest that an important factor may be a rapid fall in plasma osmolality. The possibility exists that other tissues such as the lung may also be adversely affected by rapid hypo-osmolar fluid replacement.[24,35] A prospective study comparing the mean lowest estimated plasma osmolality in children treated for ketoacidosis with replacement solutions close to the patient's plasma osmolality during the first 12 h with historical controls treated with conventional fluid replacement showed that prevention of hypo-osmolality could be achieved and was associated with prevention of clinically significant cerebral oedema.[12] This study was too small to provide statistically significant results, but it does indicate an advantage in not using hypo-osmolar solutions.

Retrospective data suggest that rapid replacement of fluids (greater than 4 L/m^2 per 24 h) adversely affects brain water content. A prospective study has suggested that slower rates of fluid replacement are more effective in treating the metabolic disturbances of ketoacidosis than rapid rates.[36] In a randomised prospective study, patients with ketoacidosis without extensive volume depletion were given either 1000 mL/h of normal saline for 4 h followed by 500 mL/h for 4 h or half those rates of normal saline over the same time interval. Those patients receiving the slower rate of fluid replacement had a more rapid correction of plasma bicarbonate, a less rapid rise in serum sodium, and less hyperchloraemia. These data support the notion of a replacement schedule of 1000 mL normal saline in the initial hour of treatment followed by 500 mL/h for an additional 8 h.[4]

Available data suggest that in the absence of significant circulatory insufficiency, there is no advantage to rapid fluid replacement. Likewise, there are no data to support the use of hypotonic solutions in the initial management of the fluid deficit of patients with diabetic ketoacidosis. Indeed, it is more reasonable to advocate the use of normal saline at rates that will restore fluid deficits in 12–24 h (infants and children, 48 h), rather than in 8 h. If the calculated or actual serum sodium concentration exceeds 150 mmol/L, most investigators advocate giving 0·45% saline instead of normal saline. The free-water deficit that always exceeds the electrolyte deficiency is corrected later with the administration of intravenous glucose to maintain plasma glucose at 14 mmol/L.

Rapid replacement with normal saline and colloid solutions is indicated for clinically significant circulatory insufficiency.

Insulin administration

Methods of administering insulin in diabetic ketoacidosis have been studied extensively. There is no place for the administration of large doses of subcutaneous insulin in this disorder. Published studies show that the continuous infusion of modest doses of insulin (5 U/h in normal saline) gives the most consistent beneficial results.[31,32] Blood glucose must be measured hourly. This relatively low dose of insulin will restore glycaemia at a rate that limits rapid changes in plasma osmolality. Moreover, potassium and phosphate move into cells at a modest rate. The actual rate of fall in blood glucose has not been validated by appropriate studies. A decrement of 5 mmol/L per h is a worthy goal, but cannot be used exclusively since the restoration of normal pH and total plasma bicarbonate are more realistic goals than euglycaemia. If blood glucose is not falling at the desired rate, and acidosis is not corrected to its target level, the rate of insulin infusion should be raised or lowered accordingly. Blood glucose must not be allowed to fall below 14 mmol/L in the first 24 h or until ketoacidosis has resolved. It should be maintained by an infusion of 5% glucose in water.

A safe alternative to continuous intravenous insulin administration is low-dose intermittent intramuscular insulin. Usually a loading dose of 10–20 units is followed by 5 units/h until plasma glucose reaches 14 mmol/L and ketoacidosis has resolved. Intramuscular insulin cannot be given when tissue perfusion is poor.

Potassium replacement

20–40 mEq/L are administered as soon as it is known that the serum potassium is not increased and that adequate renal output has been established.[4,27] Potassium replacement is monitored by measurement of serum potassium concentrations, which should be maintained $\geq$4·0 mEq/L.

Phosphate replacement

Phosphate replacement should be started if clinically significant hypophosphataemia develops. The routine use of phosphate supplementation has not been shown to be clinically beneficial. If phosphate supplementation is given, hypocalcaemia must be avoided.

Alkali treatment

The use of bicarbonate in the management of diabetic ketoacidosis is an enigma. Virtually all investigators expound on the detrimental effects of acidosis on cardiac and respiratory function and propose the prevention of circulatory and respiratory collapse as a rationale for using intravenous sodium bicarbonate for pH<7·1. Potential disadvantages of sodium bicarbonate are the greater incidence of hypokalaemia, paradoxical cerebrospinal fluid acidosis, and hypoxia.[37–41]

Several studies have failed to show any objective benefit with sodium bicarbonate treatment in patients with

diabetic ketoacidosis. The rate of correction of metabolic defects (fall in blood glucose, ketones, and lactate and increase in blood pH and total bicarbonate) were either not altered[40] or delayed[39,41] in patients with arterial blood pH 6·85–7·18. Despite the overwhelming negative data, bicarbonate treatment is still recommended for patients with arterial blood pH<7·1. There seems to be no valid reason for such recommendations and perhaps sodium bicarbonate therapy should be reserved for those patients who present with impending cardiovascular collapse. If bicarbonate is given, the usual dose is 50–100 mEq sodium bicarbonate in 250–1000 mL 0·45% saline, given over 30–60 min with 10–20 mEq of added potassium.

Low-dose heparin therapy

Since much morbidity and mortality in ketoacidosis is due to thromboembolic disease in older patients, the use of low-dose heparin for prophylaxis is important. Nevertheless, there are no data from controlled randomised studies.

Management of cerebral oedema

Cerebral oedema develops suddenly and progresses rapidly. The diagnosis is suspected by the development of severe headache and deterioration in conscious level. Computed tomographic scans and magnetic resonance imaging of the brain show characteristic abnormalities. Treatment must be initiated immediately and consists of intravenous mannitol. Recommended doses are 0·5–2·0 g/kg body weight,[11,18] repeated as necessary. Neither dexamethasone nor hyperventilation have been shown to be helpful. One series of 11 patients reported survival in 7 and normal function in 5 of 8 patients treated immediately (and repeated as needed) with 1·0 g mannitol/kg body weight intravenously.[11]

Patient education

Prevention of recurrence should be a goal of every treatment regimen. This aim can be achieved with teaching the principles of insulin treatment, blood glucose and urine ketone monitoring, and "sick day" management skills. Analysis of the cause of ketoacidosis in the individual patient may reveal appropriate areas of education that need to be emphasised.

Conclusion

Few advances have been made in the management of diabetic ketoacidosis during the past 15 years. This disorder is increasing in incidence, affecting more diverse populations, and continuing to cause significant morbidity and mortality. Many problems remain unresolved. For example, the nature, universality, and clinical importance of intracellular oedema, of which cerebral oedema may be only one component; the appropriate type and rate of fluid replacement that should be used; the importance of correcting other electrolyte disturbances, such as magnesium and phosphate; better methods to prevent thromboembolic complications; more effective management of associated infections; and the incidence and clinical importance of diabetic ketoacidosis in non-caucasian type II diabetic patients.

Since diabetic ketoacidosis has such diverse clinical features, and its various complications occur relatively infrequently, it is unlikely that significant changes in clinical management can be gleaned from studies including fewer than 100 patients. Large, well designed, multicentre trials are necessary to answer most of the questions that have been raised. The issues are important and the potential benefits worthwhile.

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Predictive ability of meta-analyses of randomised controlled trials

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Summary

Although meta-analysis of randomised clinical trials is increasingly used, the evaluation of its ability to predict the results of large trials is not available. We have calculated the relative risks (and 95% confidence intervals) for thirty meta-analyses of different interventions in perinatal medicine, covering 185 randomised controlled trials, but with the largest trial removed. We then compared those results with the result of the largest trial (total sample size more than 1000) done on that intervention and outcome. Twenty-four meta-analyses correctly predicted the direction of the treatment effect, but only eighteen of the thirty were the same both in direction of treatment effect and in statistical significance as the largest trial. There was moderate agreement, beyond chance, between meta-analysis and largest trial results (kappa statistic 0·46–0·53). A meta-analysis demonstrating a protective effect from an intervention of more than 40% had a 60% probability of correctly predicting results of the same magnitude of the largest trial. Researchers and funding agencies may use meta-analysis before recommending a clinical practice or to summarise results of three controlled trials before deciding on additional studies of promising interventions. However, further evaluation of the meta-analytical method is needed if the qualitative and quantitative results it yields are to be better understood.

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See Commentary page 741

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Introduction

Since its first application to observational studies[1,2] and more recently to randomised trials[3] meta-analysis has been increasingly used to evaluate medical interventions. However, this approach has several limitations[4,5] and its predictive ability has been questioned.[6] We need more empirical evidence of the predictive power of meta-analysis;[5,7,8] surprisingly, very little information is available on how results from meta-analyses of several small trials are confirmed or refuted by large trials,[8–10] the usually accepted "gold standard". We have compared meta-analyses of smaller studies with the corresponding results of the largest randomised trials, for the principal outcome of these studies, in the hope that the systematic evaluation will contribute to a more objective assessment of its properties.

Materials and methods

Database

We did thirty meta-analyses including a total of 185 randomised controlled trials (RCT) obtained from the pregnancy and childbirth module of the Cochrane database.[11] Our calculations differ from those in the Cochrane reviews because we excluded the largest trial for each topic, using that for the comparisons.

The Cochrane systematic reviews for pregnancy and childbirth were done with standard methodology.[12] Detailed guidelines had been sent to the teams doing the meta-analysis, describing how to select appropriate randomised trials. Authors were then asked to make a priori judgments on trials that might be grouped. The individual trials included in each review were considered by the module's editors to be reasonably similar in terms of the characteristics of the pregnancies included, the interventions compared, and the outcomes examined.[12] (Specific comments on individual trials in every review are available.[11]) The methodological quality of trials was evaluated on a simplified scheme, looking at the control of selection bias on study entry and after entry and the control of bias in assessing outcomes.[12,13]

We updated four systematic reviews, using the same methodology, to include the latest publication up to December, 1993.* The four topics were: antiplatelet agents to prevent pre-eclampsia, routine ultrasound scans to reduce perinatal mortality, routine episiotomy to prevent perineal tears, and routine electronic fetal monitoring to reduce perinatal mortality.

*References obtainable from JV