ORIGINAL ARTICLE

WHO guidelines for severe malnutrition: are they feasible in rural African hospitals?

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Aims: To assess the feasibility of implementing and sustaining the WHO guidelines for inpatient management of severe malnutrition in under-resourced rural South African hospitals, and to identify any constraints. Intervention: Three 2-day training workshops were held in 1998, followed by monthly 1-day visits for 5 months, ending in March 1999, in two rural district hospitals with limited resources in Eastern Cape Province, South Africa.

Methods: A 12-month observational study was conducted from April 2000 to April 2001 in Mary Theresa and Sipetu hospitals (Eastern Cape Province, South Africa), including 1011 child-hours of observation on the wards, medical record reviews, interviews with carers and staff, and inventories of essential supplies. All admissions (n = 193) for severe malnutrition to the two hospitals were studied. The main outcomes were the extent to which the 10 steps for routine care of severely malnourished children were implemented, proficiency of performance and constraining factors.

Results: The hospitals made the changes required in clinical and dietary management, but the tasks were not always performed fully or with sufficient care. Play and stimulation and an effective system of follow-up were not implemented. Doctors' poor knowledge, nurses' inattentiveness and insufficient interaction with carers were constraints to optimal management. The underlying factors were inadequate undergraduate training, understaffing, high doctor turnover and low morale.

Conclusions: Guidelines for severe malnutrition are largely feasible but training workshops are insufficient to achieve optimal management as staff turnover and an unsupportive health system erode the gains made and doctors treat cases without having being trained. Medical and nursing curricula in Africa must include treatment of severe malnutrition.

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alnutrition contributes to 50–60% of all child deaths. In hospitals in developing countries, severely malnourished children comprise a significant proportion of paediatric deaths, owing at least in part to unacceptably high case-fatality rates. To improve the quality of hospital care and reduce child deaths, WHO has developed case-management guidelines. The WHO working group on referral care, while endorsing the malnutrition guidelines, raised concerns about their feasibility in some settings, especially in small rural African hospitals with limited resources. This study was therefore developed to test the feasibility of implementing and sustaining the guidelines in these types of hospital and to identify factors that constrain implementation. A further aim was to assess the impact of the guidelines on case-fatality rates, and this has been reported previously.

The guidelines

Severely malnourished children undergo physiological and metabolic changes to conserve energy and preserve essential processes,⁵ including reductions in the functional capacity of organs and slowing of cellular activities. Coexisting infections add to the difficulty of maintaining metabolic control. Infections may be silent as normal immune responses are often suppressed. These profound changes put severely malnourished children at risk of death from hypoglycaemia, hypothermia, electrolyte imbalance, heart failure and untreated infection. Thus, severely malnourished children are prioritised for immediate admission, and the initial stabilisation phase focuses on frequent feeding day and night, rehydrating with low-sodium fluids with close monitoring for signs of fluid

overload, correcting electrolyte and micronutrient imbalances, and prescribing broad-spectrum antibiotics even when clinical signs are absent. The rehabilitation phase focuses on rebuilding wasted tissues, psychosocial stimulation and preparation for follow-up after discharge. In total, the guidelines set out 10 steps for routine case management.

METHODS Study site

The study took place during 2000–1 at Mary Theresa and Sipetu hospitals, which are about 280 km south west of Durban in Eastern Cape Province, South Africa, and are within the former homeland of Transkei. These are rural, under-resourced, understaffed, first-level referral hospitals with 170 and 150 beds, respectively, and serve an estimated population of 280 000. Four doctors are allocated to Mary Theresa and three to Sipetu, but this quota was rarely achieved during the study period. During the day, there are usually three nurses and two assistants in the paediatric ward at Mary Theresa (30 beds), and two nurses and one assistant at Sipetu (19 beds). At night, both have two nurses. The ward at Sipetu is often overcrowded, hence bed occupancy exceeds 100%.

Before intervention, none of the 10 steps was adequately practised. Children were not fed at night, those with diarrhoea received intravenous fluids indiscriminately, antibiotics were not given routinely, electrolyte and micronutrient deficiencies were not corrected, and children with oedema were wrongly prescribed diuretics. Consequently, case-fatality rates were unacceptably high (46% at Mary Theresa and 25% at Sipetu).⁴

Intervention to implement the guidelines

The intervention comprised three 2-day training workshops in 1998, attended by doctors, senior paediatric nurses, and key hospital and regional administrators, followed by monthly 1-day visits for 5 months, ending in March 1999. The training approach was participatory and problem-oriented. Two adaptations to the guidelines were agreed: (1) a uniform schedule of 3-hourly feeds; (2) continued use of South African oral rehydration solution, as its sodium content (60 mmol/l) was considered sufficiently similar to that recommended (45 mmol/l).

Subjects

All admissions for malnutrition (n = 193) to the two hospitals between 10 April 2000 and 9 April 2001 were enrolled into the study. Re-admissions (n = 9) were treated as new cases.

Data collection methods

Specific components of each of the 10 steps were studied on the basis of their clinical importance and ease of quantification, and detailed check-lists were developed and pre-tested. Data were collected by two researchers who (1) reviewed patients' medical records, (2) observed care practices, and (3) interviewed carers and staff. The researchers worked unobtrusively and did not influence or take part in any aspect of hospital care. Their presence did not interfere with the activities of the staff or carers.

Record reviews

Information about each child's diagnosis and treatment was abstracted using a structured form. For key initial practices, data were collected for days 1 and 3 to check consistency. The reliability of the records was checked by comparing them with observed practices.

Observations of care practices

In study months 1–5 and 10–12, approximately six unannounced visits were made to each hospital each month, including weekends and public holidays. Semistructured observations of ward practices were undertaken continuously for periods of 4 h. The total number of 4-hour ward observations were 42 in Sipetu and 43 in Mary Theresa, with equal numbers at 08:30–12:30, 13:00–17:00, 17:30–21:30, 22:00–02:00, 02:30–06:30 and 06:30–10:30. Activities observed included feeding, dispensing of drugs, monitoring vital signs, hygiene, play and education sessions for carers. Also recorded were ward conditions, staff/child contacts and activities performed by carers. Separate observations were made of admission procedures, feed preparation, ward rounds and

Table 1 Number of observations undertaken Mary Theresa Observation sessions Sipetu Ward activities (4-h sessions) Day (06:30-10:30; 08:30-12:30; 13:00-21 21 Evening (17:30-21:30) Night (22:00-02:00 and 02:30-06:30) 14 15 Total number of 4-h ward observations 42 43 Number at weekends (day/evening/night) 5 6 Doctors' ward rounds 15 16 Nursing shift handovers 13 10 Daily weighing and plotting 21 14 Feed preparation 12 8 Admission procedure (in outpatients) 5 2 Arrival on ward 13 3

handovers between shifts. Table 1 shows the number and types of observations. There were 1011 child-hours of ward observation, including 356 mealtimes.

Carer interviews

Interviews were conducted with carers of every alternate admission to validate information from the record reviews and ascertain waiting times before admission. Interviews were conducted in Xhosa, the local language. Thirty carers were also visited 1 and 6 months after discharge to obtain information about follow-up.

Staff interviews

Opinions about the guidelines and barriers to implementation were sought through focus group discussions with nurses and interviews with doctors. At the end of the study, findings were presented to hospital staff, and shortcomings in care were discussed in a frank and open manner. Staff were invited to express their point of view if they disagreed with any of the findings or conclusions drawn.

Inventory of supplies

Every 2 months, except in month 9, the availability of essential drugs and supplies, ingredients for feeds and equipment was checked. For missing items, follow-up investigations were made to establish the reason(s), actions taken and response.

Ethical permission

Permission was granted for the study by ethical committees of the London School of Hygiene and Tropical Medicine, London, UK and the University of the Western Cape, Bellville, South Africa.

Data quality

Two researchers (NK and NS) collected and entered all the data. Interobserver agreement was checked before the study by both researchers abstracting data from the same records independently and both observing the same children simultaneously. Training continued until agreement reached at least 93%. This process was repeated in month 6 with similar agreement.

Analysis

Double data entry was verified using EPI-INFO 6.04 (CDC Atlanta, Georgia, USA). We defined a step as "feasible" if the main components were implemented, whether or not they were perfectly performed.

Table 2 Availability of essential supplies (times in stock during five checks)

ltem	Sipetu	Mary Theresa
Potassium (KCl or slow K)	5	5
Magnesium (mix or MgSO ₄)	5	4
Co-trimoxazole	4	3
Ampicillin	4	5
Gentamicin	5	5
Oxygen	4	5
Vitamin A	5	4
Multivitamins	5	4
Folic acid	3	1
Zinc, copper	2	3
lron I	5	4

RESULTS

Patient characteristics

No mother/carer refused to participate. Children in both hospitals were of similar age and anthropometric status.⁴ Their mean (SD) age was 17 (14) months. Mean (SD) weight-for-length Z score was –1.5 (1.1), 42% had oedema, and 32% had skin lesions. At Mary Theresa, 21% died during 2000–1. At Sipetu, 18% died during April–December 2000, but this rose to 38% when doctors untrained in treating malnutrition replaced trained doctors.⁴

Staffing

Senior paediatric nursing staff remained the same at both hospitals throughout the study, as did the medical staff at Mary Theresa. At Sipetu, doctor turnover was considerable. Doctors were overstretched: sometimes just one had responsibility for all inpatients, outpatients and emergencies.

Essential supplies

Before intervention, many basic resources were absent. During the study, the main shortfalls were folic acid, zinc and copper (table 2), and to a lesser extent oil for feeds and some antibiotics. The reasons were inadequate ordering by ward staff and distribution problems from the central medical stores. Drugs were sometimes wrongly reported as out of stock by pharmacy staff who were unaware of their alternative names.

Feasibility

Table 3 shows the extent to which specific components of the guidelines were implemented. The performance of each step and of triage are described below.

Triage

Little improvement was observed in queuing time. Children were seen consecutively, first by a nurse and then by a doctor: at Sipetu, carers had to answer a health question correctly before being allowed to see the nurse. Health education talks further lengthened the admission process. Doctors saw the children after completing their ward rounds, usually in the afternoon. Some were then sent for an *x*-ray examination and had to queue for the doctor again before being admitted.

Step 1: treat/prevent hypoglycaemia

Both hospitals successfully changed from three meals to eight specially prepared milk-based feeds (F-75). Most children were fed every 3 h and half were fed within 1 h of admission (table 3). A glucometer was provided for Mary Theresa hospital but was rarely used, mainly owing to the junior nurses' lack of confidence with new equipment.

Step 2: treat/prevent hypothermia

Substantial organisational changes were required to create a warm environment for malnourished children. Both hospitals arranged a separate room and electric heaters, but the room temperature at Sipetu was erratic (table 3) owing to power failures. Carers were encouraged to sleep with their children on mattresses on the floor. Blankets were provided, but linen shortage was common, and children sometimes lay in wet sheets for several hours. Identification and treatment of hypothermia was poor. Temperatures were rarely checked on admission to the ward and no routine measurements were made at Mary Theresa, although contrived readings were recorded five times a day. Nurses touched the children infrequently, so those who were cold were rarely identified.

Step 3: prevent/treat dehydration

The indiscriminate practice of rehydrating intravenously ceased with the introduction of the guidelines, but when intravenous rehydration was prescribed, doctors' orders were unclear, nurses rarely recorded having given it, and pulse and respiration rates were never monitored. Also, carers were observed altering the drip rate. Carers were often made responsible for giving oral rehydration solution, but without guidance about volume or frequency. Carers failed to report vomiting and diarrhoea, hence children in danger of dehydration were rarely identified.

Step 4: correct electrolyte imbalance

After intervention, children were no longer prescribed diuretics for oedema and were receiving potassium, either as KCl solution or as crushed "Slow-K" tablets. A "mineral mix" solution containing magnesium was distributed to the hospitals and, when unavailable, injectable magnesium sulphate was given orally. The main problems were non-prescribing of potassium by some doctors, and errors in calculating doses.

Step 5: treat infection

During the study, 90% of children received antibiotics routinely from day 1, but only about half received the WHO recommended combinations either because they were out of stock or had not been prescribed. At Sipetu, inexperienced doctors with little training in severe malnutrition prescribed antibiotics with Gram-negative cover less frequently than trained doctors (15% vs 46%, p<0.001). This was accompanied by a dramatic rise in deaths due to sepsis.⁴ In both hospitals, some night staff administered antibiotics several hours before they were due, but signed as though they had given them on time. Despite creating a separate room, crowding was still a problem, especially at Sipetu where children often had to share beds. Hygiene practices were poor, particularly among carers, and the malnutrition room at Sipetu had no sink.

Step 6: correct micronutrient deficiencies

Vitamin A, folic acid and multivitamins were provided to most children at Sipetu but fewer children at Mary Theresa (table 3). Doctors did not always follow the age-specific doses for vitamin A, and over half the children received an incorrect dose. Nurses at one hospital gave a daily high dose of vitamin A instead of a single high dose until stopped by the research team. Only 46% of children received zinc and copper, as the mineral mix solution was supplied intermittently. Iron was correctly withheld in the stabilisation phase but was rarely prescribed during the rehabilitation phase.

Steps 7 and 8: feed cautiously and rebuild wasted tissues

Approximately 90% of children received F-75 and F-100. The hospital provided the milk, sugar and oil, and the ward nurses prepared the feeds, but their reluctance to use an electric whisk caused the oil to separate out. The volume of F-75 was determined correctly for >80% of children in Sipetu, but for only 46% in Mary Theresa owing to errors in reading the chart. Nurses on both wards incorrectly reduced the volume of F-75 if a child lost weight. Both hospitals developed a 24-h intake form. Carers were often responsible for dispensing feeds but were poorly supervised; consequently, children with insufficient intake who should have been fed nasogastrically went unnoticed. Some carers gave food from their own plate, or food brought from outside. Transition to the rehabilitation phase was haphazard and about 70% of children were transferred too soon or too late. Children in the rehabilitation phase were rarely fed until full. Doctors were generally not involved in decisions concerning feeding.

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	C=carer interviews; O, observations; R, record reviews;		

Step 9: provide stimulation, play and loving care

Nurses were usually caring in their interactions with the children, but these were very brief, averaging about 5 min per 4-h observation. Few toys and no developmental play sessions were observed, and staff did not encourage carers to interact with their children.

Step 10: prepare for follow-up

Education sessions were sporadic, and there was inadequate discussion with carers about resources at home and about what to feed the child. More than half the carers received a referral letter and most took it to the local clinic. However, some clinic staff were unwelcoming and sometimes clinics were closed:

Table 4 Omissions in care*, constraints to optimal management and locus of responsibility Omissions in care Constraints to optimal management DOCTORS/NURSES/MANAGERS Absent Outpatient staff unaware that severe malnutrition cases have priority Hypoglycaemia children not fed by feeds unsupervised; intakes unreliable NG tube when intake <80% of target carers do not know they should report if danger signs overlooked child becomes drowsy Hypothermia NURSES minimal nurse/child contact cold children overlooked poor basic nursing skills; temperatures danger signs not measured overlooked carers do not know to report cold child children left wet linen shortage; linen locked away at no active rewarming night DOCTORS Dehydration/overhydration inadequate fluid no daily ward round management during rehydration instructions to nurses new/continuing episodes of diarrhoea no instructions to nurses to monitor child fluid overload not during rehydration to prevent fluid prevented overload incorrect fluid volumes prescribed NURSES carers fail to report diarrhoea/vomiting carers use ORS without supervision, tamper with intravenous fluids ORS volume not recorded child not monitored when given intravenous fluid or oral fluids Electrolyte imbalance **DOCTORS** lack of knowledge that potassium is potassium, magnesium not prescribed essential poor labelling of bottles; doses on incorrect amounts prescribed bottles unclear

Infection/sepsis

- gentamicin not prescribed
- incorrect amounts of antibiotics prescribed
- drugs not dispensed on time
- poor hygiene

Feeding

no check to see if child is fed appropriately

DOCTORS

lack of knowledge that aggressive antibiotic treatment is necessary when child has complications

- poor basic nursing skills; poor motivation
- re-ordering left too late

DOCTORS

- unaware of the central role that feeding has in recovery
- not seen as doctors' role

*Omissions in bold are those that were considered a primary factor for deaths in 2000-1.5

only one-third of the children were weighed regularly. Clinic staff lacked awareness of the follow-up programme and failed to reinforce nutrition or health messages.

Constraints

Table 4 shows the constraints to optimal management and the locus of responsibility, focusing on those components that are most important for survival. The most critical omissions in care were inadequate fluid management and failure to prescribe potassium and gentamicin. The key constraints were lack of knowledge among doctors, nurses' inattentiveness and insufficient communication between staff and carers.

DISCUSSION

Malnutrition is the main contributor to the burden of disease in childhood.17 Although there are as many deaths from the potentiating effects of malnutrition as from AIDS, tuberculosis and malaria (6 million/year), malnutrition fails to receive the attention it warrants in health policies and resource allocation. Childhood malnutrition has increased in sub-Saharan Africa with rising poverty, food insecurity and HIV/AIDS, and is likely to escalate further as the HIV epidemic worsens. In hospitals, severe malnutrition remains poorly managed, yet effective treatment has been known for 50 years.8 Although severe malnutrition may not always rank high among hospital admissions, it represents a disproportionate percentage of deaths. For example, during January-June 2004, in 11 hospitals in Eastern Cape Province, severe malnutrition accounted for 15% of paediatric admissions but 33% of deaths. Its importance in child mortality is insufficiently acknowledged.

We found that preparation of the special milk formulations and round-the-clock feeding could be implemented in poorly resourced district hospitals and that the guidelines were largely feasible despite the major changes that were required in nursing, medical and administrative routines. Other problems, however, constrained their full implementation (table 4), especially doctors' poor knowledge, nurses' inattentiveness, and poor communication among staff and between nurses and carers. Poor knowledge of malnutrition was particularly evident in Sipetu, where, 2 years after providing in-service training, high doctor turnover and an unsupportive health system eroded the gains made, and inexperienced incoming doctors were responsible for treating severe malnutrition without having been adequately trained.

What is the role of the paediatric community in addressing the factors that constrain improved care? Many of the constraints could be dealt with. Sepsis was the presumed cause of 20/46 deaths, and electrolyte imbalance of four deaths.4 The main responsibility for preventing these deaths lies with doctors. Strict adherence to the guidelines for antibiotics, potassium and magnesium would, we believe, prevent most deaths from these causes and could be achieved through training, standing orders and support and supervision of inexperienced doctors. Thirteen deaths were attributed to poor fluid management.4 To prevent such deaths, doctors should review fluid management daily for all children with diarrhoea and give clear instructions about rehydration. Wall charts in the emergency room could remind staff of the special procedures for treatment of shock. Doctors should reinforce the importance of nurses monitoring pulse and respirations to prevent fluid overload during rehydration and taking steps to prevent dehydration during new or continuing episodes. Although the main responsibility for preventing hypoglycaemia and hypothermia lies with nurses, doctors could play a role if their understanding was improved by ensuring that key practices are followed. Doctors should take the lead in establishing auditand-feedback meetings with nurses and managers and, when appropriate, include pharmacy and other staff and patients' representative(s).

Underlying the constraints to optimal management were inadequate undergraduate training of doctors, and lack of support and supervision. The paediatric community has a responsibility to ensure that WHO malnutrition guidelines are included in paediatric texts and in medical and nursing curricula, especially in Africa and Asia, and that newly qualified doctors receive support and supervision particularly when assigned to rural hospitals. Paediatricians should be responsible for ensuring that the guidelines are implemented in all teaching hospitals so that trainee doctors and nurses can learn through supervised practice.

Other constraints to optimal management were understaffing, stress, low morale and high staff turnover. Nurses cited staff shortages as a reason for some shortcomings, and late salary payments, inadequate pay rises and non-recognition of additional training they had gained for lack of commitment among some staff. These grievances are well recognised as affecting quality of care9 and need to be addressed by the Department of Health. On the whole, however, nursing staff reported that efforts to implement the guidelines had increased self-esteem and motivation. Improving staff retention will require action on several fronts. Common "push" factors, especially in rural hospitals, are low salaries, poor living conditions and poor job satisfaction stemming from inadequate resources.10 In some African countries, working conditions are more adverse than in South Africa, with high child:nurse ratios that are incompatible with high-quality performance. Little is known about the response of health staff to different types of incentives or monitoring strategies, or whether such strategies improve job performance.11 12 Staff shortage and high turnover are linked with outward migration of doctors and nurses to rich countries, and the damage migration causes to already inadequate health systems in sub-Saharan Africa has been highlighted recently.13 14 Among the "pull" factors, UK work permits were approved for 5880 South African health professionals in 2003, and the financial cost to South Africa of this "brain drain" is estimated at \$37 million.13 Although the UK National Health Service does not actively recruit doctors and nurses from South Africa, the recruitment code is voluntary and is not enforced, and individual employers may bypass the code and recruit directly. Neither Australia, the UK nor the USA train sufficient doctors or nurses to meet their needs, and a shift in training policy by rich countries is clearly needed, as well as mandatory recruitment codes that apply to both public and private agencies.

Doctors were overstretched. Some tasks could have been done by nurses, but their activities are closely delineated by the Nursing Council, which precludes putting up intravenous infusions and prescribing antibiotics and electrolyte solutions. Professional bodies need to reconsider how best to meet the healthcare needs of patients in resource-poor communities. This might include development of nurse practitioners to augment the role of doctors' and other cadres for specific tasks, such as teaching mothers about improved home-feeding and play.

Nursing staff expected carers to participate in treatment tasks, including rehydration and feeding, but failed to explain why and how this should be done or to supervise them. The reproachful attitudes of some staff, and failure to listen to carers' concerns, discouraged carers from seeking help. Carers are an important resource, and better communication between nurses and carers might improve cooperation and promote an effective partnership.¹⁵ Daily care rested heavily with junior nursing staff. Their responsibilities highlight the need to improve their training. In the short term, greater emphasis on supervised practice could resolve some of the weaknesses. In-service training should be widened to include outpatient and pharmacy staff, and health workers at primary care clinics and their managers.

Community-based therapeutic care for severely malnourished children is currently receiving prominence. This approach offers several advantages, including high coverage and early detection before the onset of acute illness. Malnourished children without complications are treated at home with weekly or fortnightly supervision; those with complications are referred to inpatient care, but can be discharged early for continuing care in the community. Results are encouraging: more than 22 000 children have been treated in this way in Malawi, Ethiopia and Sudan, with a case-fatality rate of 4.8%. Most of the experience lies in humanitarian emergencies, where leadership is provided by

What is already known on this topic

- Severe malnutrition is an important cause of child death in hospitals in developing countries.
- Treatment needs improving as case-fatality rates of 20– 40% are not unusual.
- WHO has developed guidelines to improve case management in hospitals.

What this study adds

- WHO guidelines for severe malnutrition are largely feasible even in small rural hospitals with limited resources.
- Training workshops can improve case management but need to be supported by other interventions that build human capital, reduce outward migration and strengthen health systems.
- Medical and nursing curricula in Africa must include treatment of severe malnutrition.

highly skilled and motivated staff, mostly from external agencies. The approach requires active case-finding and distribution of energy-dense, micronutrient-enriched, ready-to-use therapeutic food. Implementing community-based therapeutic care within routine health services will require functioning infrastructures and resources at the district level. Insufficient investment and health system constraints, however, are severely limiting community care, as is evident in the stagnation of national health worker training at <10% in most countries implementing the WHO programme of Integrated Management of Childhood Illness.¹⁷

In conclusion, severe malnutrition is an important, but often disregarded, cause of child death in hospitals in developing countries. Treatment is straightforward, and humanitarian relief agencies achieve excellent results with their specially trained staff. In contrast, treatment is neglected in medical and nursing undergraduate education and specialist paediatric training in most countries and in mainstream paediatric texts. Consequently, mismanagement is commonplace within national health services, and South Africa is no exception. We found that case management can be improved, though not fully, through in-service training and support, but other interventions are needed to build human capital and mitigate the brain drain of doctors and nurses.

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ARCHIVIST.....

Progress in pre-eclampsia research

■he leading cause of preterm delivery in the world is pre-eclampsia. Some 3–5% of pregnancies are complicated by pre-eclampsia, and it is a major factor in maternal and neonatal morbidity and mortality. Endothelial dysfunction seems to be a fundamental problem in pre-eclampsia, and recent animal and human research on proangiogenic and antiangiogenic proteins has raised hopes of understanding, predicting, and even preventing or treating the condition.

The research has concentrated on two antiangiogenic proteins that act in different ways: soluble fms-like tyrosine kinase 1 (sFlt1; also known as soluble vascular endothelial growth factor receptor 1, a protein that binds the proangiogenic proteins, placental growth factor (PIGF) and vascular endothelial growth factor, and soluble endoglin, a co-receptor for transforming growth factor β_1 and β_3 . The genes for both sFlt1 and endoglin are upregulated in the placentas of women with preeclampsia. In rats, overexpression of the gene for sFlt1 gives rise to some of the features of preeclampsia, but overexpression of the genes for both sFlt1 and soluble endoglin produces a full-blown picture of severe disease with severe hypertension, heavy proteinuria, elevated liver enzyme concentrations and evidence of microangiopathy (circulating schistocytes).

Now researchers in the USA (New England Journal of Medicine 2006; 355:992-1005; see also Editorial, ibid: 1056-8) have provided human data to support the animal research findings. They used saved blood samples from 552 women in a 1992-5 pre-eclampsia prevention trial and found that concentrations of endoglin began to increase about 2 or 3 months before the onset of clinical pre-eclampsia. Among women who developed pre-eclampsia at term, levels were raised from 25-28 weeks, and among women who developed preterm pre-eclampsia, they were raised from 17-20 weeks. Increased endoglin was usually accompanied by an increased sFlt1:PIGF ratio, and the greatest predictor of pre-eclampsia was the combination of high endoglin and high sFlt1:PIGF ratio. In normal pregnancies, endoglin concentrations also increased, but to a lesser extent, during the last 2 months.

The World Health Organisation has set up a trial to evaluate the usefulness of these measures in predicting pre-eclampsia in developing countries. Further studies in sFlt1-upregulated rats have suggested that VEGF-121 might reverse the features of pre-eclampsia.