Radioiodine treatment of hyperthyroidism

Duration of radioprotective effects of antithyroid drug therapy is still not clear

DR M A ANSARY/SPL

RESEARCH p 514

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In this week's *BMJ*, Walter and colleagues[1] present a systematic review and meta-analysis of randomised controlled trials of the effects of antithyroid drugs on treatment with radioiodine. Radioiodine is perceived as a simple and cost effective treatment of hyperthyroidism.[2] A β adrenergic blocker, such as propranolol (total daily dose of 80-160 mg), can usually provide appreciable relief of symptoms between the initial consultation and administration of radioiodine, and for the next six to eight weeks until treatment is effective.

In elderly patients and in those with severe thyrotoxicosis or cardiovascular complications, such as atrial fibrillation and heart failure, it is common practice to restore euthyroidism first with antithyroid drugs. This prevents the rare, but well recognised, worsening of hyperthyroidism caused by irradiation induced leakage of stored thyroid hormones seen within the first few days,[3] an important consideration given the increased mortality in the early weeks after giving radioiodine.[4]

Antithyroid drugs do not prevent an increase in serum thyroid hormone concentrations, but any increase is from a lower baseline and has no clinical relevance.[5] The other advantage of pretreatment with antithyroid drugs in severe hyperthyroidism, when the concentration of free thyroxine in the serum is usually more than 60 pmol/l (normal 10-25), is that a rational discussion about the treatment options is more likely when the patient is euthyroid and, therefore, less agitated and more able to concentrate. In a survey of members of the American Thyroid Association, 31% of correspondents prescribed antithyroid drugs before and 40% after radioiodine treatment for patients with Graves' disease.[6] The role of antithyroid drugs after radioiodine is simply to buy time until that treatment is effective.

Considerable experience has been gained in using antithyroid drugs as an adjunct to radioiodine treatment in the past 50 years or so, but controversy remains about whether carbimazole (and its active metabolite, methimazole) and propylthiouracil influence the actions of radioiodine. To some extent this confusion is a reflection of the retrospective nature of many of the studies, most of which are small; patient selection; the type of hyperthyroidism (Graves' disease or toxic nodular goitre) studied; the likelihood that antithyroid drugs were given before and after radioiodine to patients with the most severe disease; the various radioiodine dosage regimens used; and the fact that thyroid status at the time of treatment may alter iodine kinetics and the effectiveness of radioiodine. Many of these difficulties were identified by Walter and colleagues.[1] They found that antithyroid drugs given in the week before or after radioiodine increased the risk of treatment failure (relative risk 1.28, 95% confidence interval 1.07 to 1.52) and reduced the risk of hypothyroidism (0.68, 0.53 to 0.87). Overall the quality of evidence was poor.

Although the review is valuable in that it highlights the inadequacy of data collection over many years, the conclusions are not useful for patient management. Indeed, current beliefs, such as the radioprotective effect of propylthiouracil lasting longer than that of carbimazole,[7] were not supported by this type of analysis. So what should the clinician do while awaiting better quality trials?

For the hyperthyroid patient, judged sufficiently unwell to justify adjunctive antithyroid treatment for four to six weeks before radioiodine, it may be counterproductive to stop the drug for seven days or more either side of treatment. Evidence exists, however, that the radioprotective effect of antithyroid drugs can be overcome by increasing the dose of radioiodine, perhaps by as little as 25%.[8] A pragmatic approach, used in our clinic for several years, is to discontinue the antithyroid drug for 48 hours before and after 400 MBq radioiodine—a dose greater than that used in most of the studies under scrutiny. When re-started the antithyroid drug should be given for six weeks and thyroid status should be assessed at eight weeks. Failure to achieve euthyroidism or an appreciable improvement in hyperthyroidism is an indication for further radioiodine.

Although radioiodine is increasingly the treatment of choice in patients with hyperthyroidism due to Graves' disease, we need to be more cautious about a treatment that almost always causes hypothyroidism, especially when we have no consensus on what constitutes correct thyroid hormone replacement.[9] Some patients abhor the idea of any form of irradiation. In addition, radioiodine, rather than antithyroid drugs or surgery, is most closely associated with a deterioration in ophthalmopathy, a risk that can be reduced by concomitant treatment with steroids.[10] Patients worry that they will gain excessive weight if rendered hypothyroid, and this may be true if serum concentrations of thyroid stimulating hormone are simply restored to the reference range with thyroxine.[11]

Of some concern are the recent reports that radioiodine treatment itself may cause increased morbidity and mortality from cardiovascular disease.[12] Therefore, it should

be remembered that long term treatment with carbimazole for 10 years or more is a viable alternative,[13] and that subtotal thyroidectomy in experienced hands guarantees patients the longest existence without taking drugs.

1 Walter MA, Briel M, Christ-Crain M, Bonnema SJ, Connell J, Cooper DS, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2007 doi: 10.1136/bmj.39114.670150.BE.
2 Patel NN, Abraham P, Buscombe J, Vanderpump MPJ. The cost effectiveness of treatment modalities for thyrotoxicosis in a UK center. *Thyroid* 2006;16:593-8.
3 Shafer RB, Nuttall FQ. Acute changes in thyroid function in patients treated with radioactive iodine. *Lancet* 1975;ii:635-7.
4 Parker JL, Lawson DH. Death from thyrotoxicosis. *Lancet* 1973;ii:894-5.
5 Burch HB, Solomon BL, Cooper DS, Ferguson P, Walpert N, Howard R. The effect of antithyroid drug pretreatment on acute changes in thyroid hormone levels after ^{131}I ablation for Graves' disease. *J Clin Endocrinol Metab* 2001;86:3016-21.
6 Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. *J Clin Endocrinol Metab* 1990;70:1518-24.
7 Hancock LD, Tuttle RM, LeMar H, Bauman J, Patience T. The effect of propylthiouracil on subsequent radioactive iodine therapy in Graves' disease. *Clin Endocrinol* 1997;47:425-30.
8 Crooks J, Buchanan WW, Wayne EJ, MacDonald E. Effects of pre-treatment with methylthiouracil on results of ^{131}I therapy. *BMJ* 1960;1:151-4.
9 Toft A. Which thyroxine? *Thyroid* 2005;15:124-6.
10 Bartalena L. Glucocorticoids for Graves' ophthalmopathy; how and when. *J Clin Endocrinol Metab* 2005;90:5497-9.
11 Tigas S, Idiculla J, Beckett G, Toft A. Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? *Thyroid* 2000;10:1107-11.
12 Nyirenda MJ, Clark DN, Finlayson AR, Read J, Elders A, Bain M, et al. Thyroid disease and increased cardiovascular risk. *Thyroid* 2005;15:718-24.
13 Azizi F, Esmaillzadeh A, Mirmiran P, Ainy E. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. *Eur J Endocrinol* 2005;152:695-701.

Exercise in survivors of cancer

Evidence so far is promising, yet the optimal programme is unclear

ALIX/PHANIE/REX

RESEARCH p 517

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The benefits of exercise in people with cardiovascular disease are well documented,[1] but its effect in people with cancer is less well studied. This is largely because research into the effects of exercise in preventing and recovering from heart attacks and strokes has been studied for much longer.

In this week's *BMJ*, a randomised controlled trial by Mutrie and colleagues assesses the functional and psychological effects of a 12 week exercise programme in women with early stage breast cancer.[2] It found no significant difference in the primary outcome of quality of life at 12 weeks as measured by the functional assessment of cancer therapy (FACT-G) questionnaire. However, it did find significant improvements at 12 weeks in secondary outcomes such as the number of metres walked in 12 minutes, the amount of exercise of moderate intensity taken in one week, mobility of the shoulder, and breast cancer specific quality of life. Most of the effects were maintained at six months, and there were no adverse effects.

Many studies have focused on the psychological effects of exercise in people with cancer,[3] but there is increasing interest in physical outcomes as well.[4-6] For example, the first randomised controlled trial assessing weight training on mood and quality of life in survivors of breast cancer reported significant improvements in physical global scores (2.1% in the treatment group compared with a 1.2% reduction in the control group). Changes in bench press results significantly correlated with changes in physical global score and psychosocial global score.[4] Other studies have shown that exercise may improve quality of life and promote greater acceptance of physical changes associated with treatment for cancer.[7-9] A recent systematic review of the effects of exercise in people with cancer concluded that although exercise seems to be promising, the included studies had limitations.[10] Most studies were small and not randomised, only included women diagnosed with breast cancer, and studied cardiovascular exercise in favour of other forms of exercise such as strength training [10]

The trial by Mutrie and colleagues is the first to be carried out in the United Kingdom and has the largest sample size of published exercise trials in breast cancer; however, it too has limitations.[10] One such limitation is that it did not look at different subgroups of patients with breast cancer, such as those with genetically linked breast cancer, those with different oestrogen receptor status, premenopausal women, and postmenopausal women. The effectiveness of exercise may well vary within certain subgroups of patients who have had breast cancer, and this needs to be explored in future studies.

Clearly these and other outstanding questions warrant further research. For example, can exercise prevent primary malignancy and recurrence of certain cancers? One systematic review of 19 cohort and 29 case controlled studies found an inverse association between physical activity in postmenopausal women and the risk of breast cancer (20-80% reduced risk of breast cancer), compared with a more modest reduction in premenopausal women of 15-20%.[11] Other questions include what forms of exercise are the most effective in terms of cardiovascular and strength training recommendations? Could overexercising suppress the immune system and potentially be harmful to women who have had breast cancer?

On the basis of the evidence so far, exercise seems to improve the physical and mental health of women diagnosed with breast cancer. However, the optimal time to prescribe exercise and the best intensity, mode, and duration of treatment are unclear. Until further research is completed health professionals can safely recommend exercise incorporating a cardiovascular and strength training component to women with breast cancer.

1 Williams MA, Ades PA, Hamm LF, Keteyian SJ, LaFontaine TP, Roitman JL, et al. Clinical evidence for a health benefit from cardiac rehabilitation: an update. *Am Heart J* 2006;152:835-41.
2 Mutrie N, Campbell AM, Whyte F, McConnachie A, Emslie C, Lee L, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ* 2007 doi: 10.1136/bmj.39094.648553.AE.
3 Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J Clin Oncol* 2005;23:899-909.
4 Daley AJ, Mutrie N, Crank H, Coleman R, Saxton J. Exercise therapy in women who have had breast cancer: design of the Sheffield women's exercise and well-being project. *Health Educ Res* 2004;19:686-97.
5 Turner J, Hayes S, Reul-Hirche H. Improving the physical status and quality of life of women treated for breast cancer: a pilot study of structured exercise intervention. *J Surg Oncol* 2004;86:141-6.
6 Ohira R, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors: the weight training for breast cancer survivors (WTBS) study. *Cancer* 2006;106:2076-83.
7 Courneya KS. Exercise intervention during cancer treatment: biosocial outcomes. *Exerc Sport Sci Rev* 2001;29:60-4.
8 Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. *Ann Behav Med* 1999;21:171-9.
9 Courneya K, Mackey J, McKenzie D. Exercise for breast cancer survivors. *Phys Sportsmed* 2002;30:1-17.
10 Markes M, Brockow T, Resch KL. Exercise for women receiving adjuvant therapy for breast cancer. *Cochrane Database Syst Rev* 2006;(18): CD005001.
11 Monninkhof EM, Elias SG, van der Tweel I, Schuit AJ, Voskuil DW, van Leeuwen FE, et al. Physical activity and breast cancer: a systematic review. *Epidemiology* 2007;18:137-57.

Researching a good death

Raises difficult issues, but many patients are keen to participate

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RESEARCH p 521

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In this week's *BMJ*, a qualitative study by Kendall and colleagues assesses the challenges in conducting research in people nearing the end of life.[1] The study—conducted in researchers, people with cancer, and carers—provides a landmark in a challenging area, as well as offering encouragement for future researchers. It finds that many patients do wish to participate in research, and that researchers, while appreciating the challenges of conducting research in this area, think that it is no more demanding than in other areas. The study also offers potential solutions to the barriers to carrying out such research. These take the form of a useful checklist to be consulted before designing any study intended to research a good death.

A central moral point of the study is that patients must not be paternalistically excluded from researching a good death, because research can enrich the lives of participants. This perspective reflects the work of Harvey Chochinov, who has developed an empirically based psychotherapeutic interview that places illness within a life context and can enhance the dignity of patients. Ninety one of 100 patients who received the interview were satisfied with the results.[2] Integrating the enhancement of dignity into end of life research could improve the research experience of patients who are terminally ill. That some seriously ill patients have limited capacity to consent[3] must be considered when developing recruitment methods, however.

Kendall and colleagues acknowledge that their results relate mainly to people with cancer, who have a somewhat predictable illness trajectory. However, in Canada, as in other wealthy nations, only about a quarter of all deaths are due to cancer. People with other illnesses also need innovative approaches to end of life care. For example, one third of patients with heart failure will die suddenly.[4] Models of care where curative efforts are withdrawn as palliative care is escalated[5] cannot easily be applied to meet the needs of these and many other patients.

The first three barriers to end of life care listed by Kendall and colleagues are unstable definitions of end of life care and terminal care, inability to make an accurate prognosis, and variability in awareness of diagnosis and prognosis in patients and carers. These barriers hinge around uncertainty. Such uncertainty especially confounds researching a good death for patients expected to die of non-malignant disease. These patients have an uncertain prognosis and often die in hospital during a therapeutic trial.

The extreme variation in intensity of treatments provided at the end of life for patients in hospital[6] suggests that the reality of death is frequently overlooked. The tendency of doctors to overestimate survival probably contributes to a failure to focus upon providing a good death.[7] Many doctors' actions suggest that death is viewed as a failure in care rather than being inevitable.[8] Ways to overcome barriers to a good death in hospital require administrators and doctors to make end of life care a priority, as the necessary resources are readily available to most patients.

Problems at the end of life are common for family members as well as patients. Over half of all complaints to the National Health Service are about care around the time of death.[9] Harms to the family may be severe and long lasting. One study found that listening attentively to family members before the death of a patient in an intensive care unit reduced post-traumatic stress from 70% to 45% at three months.[10] Although this reduction is dramatic, a 45% rate of post-traumatic stress is hardly ideal. Future research that incorporates the challenges to researching a good death while focusing on the needs of family members would be welcome.

Patients will always have complex and conflicting needs for end of life care. A Canadian study of patients with an expected mortality rate of 50% at six months found that the most important aspect of care was having trust in their doctor. Not having the dying process unduly prolonged and having open and honest communication with the doctor were the second and third most important aspects of care.[11]

If the disparate needs of patients are to be met, if hope and trust are to be maintained while death is honestly conceived, prognostic uncertainty must not simply be managed but should be embraced. We all live with the knowledge that death is inevitable, yet our

lives can be rich and full of meaning. "Dying" patients and their families deserve the same opportunity (a recently developed frailty index[12] could help identify patients at risk of dying). Ideally, communication about death and dying should enhance the dignity of patients. Creating ways to facilitate such communication could underpin future research studies intended to help ensure a good death for all.

1 Kendall M, Harris F, Boyd K, Sheikh A, Murray SA, Brown D, et al. Key challenges and ways forward in researching the "good death": qualitative in-depth interview and focus group study. *BMJ* 2007 doi: 10.1136/bmj.39097.582639.55.
2 Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClement S, Harlos M. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. *J Clin Oncol* 2005;20;23:5520-5.
3 Cassell EJ, Leon AC, Kaufman SG. Preliminary evidence of impaired thinking in sick patients. *Ann Intern Med* 2001;134:1120-3.
4 Adamson PB, Gilbert EM. Reducing the risk of sudden death in heart failure with beta-blockers. *J Card Fail* 2006;12:734-46.
5 Murray SA, Kendall M, Boyd K, Sheikh A. Illness trajectories and palliative care. *BMJ* 2005;330:1007-11.
6 Wennberg JE, Fisher ES, Stukel TA, Skinner JS, Sharp SM, Bronner KK. Use of hospitals, physician visits, and hospice care during last six months of life among cohorts loyal to highly respected hospitals in the United States. *BMJ* 2004;328:607.
7 Christakis NA, Lamont EB. Extent and determinants of error in doctors' prognoses in terminally ill patients: prospective cohort study. *BMJ* 2000;320:469-72.
8 Middlewood S, Gardner G, Gardner A. Dying in hospital: medical failure or natural outcome? *J Pain Symptom Manage* 2001;22:1035-41.
9 Mayor S. Care of dying patients and safety dominate report on NHS complaints. *BMJ* 2007;334:278.
10 Lautrette A, Darmon M, Megarbane B, Joly LM, Chevret S, Adrie C, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med* 2007;356:469-78.
11 Heyland DK, Lavery JV, Tranmer JE, Shortt SE, Taylor SJ. Dying in Canada: is it an institutionalized, technologically supported experience? *J Palliat Care* 2000;16 suppl:S10-6.
12 Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489-95.

Ratio of boys to girls at birth

Is not related to the time taken to conceive, or exposure to environmental agents

LINDA WOODS

RESEARCH p 524

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In 2005, the *BMJ* published a paper suggesting that subfertile couples were more likely than fertile couples to have boys.[1] This observation was offered as support of the hypothesis that sperm bearing Y chromosomes swim faster through viscous cervical mucous. In the flurry of letters that followed, other researchers reported that their data did not support the sex ratio finding.[2] Furthermore, the sperm swimming hypothesis was exposed as a persistent myth.[3]

In this week's *BMJ*, Joffe and colleagues[4] pool data from several large fecundity studies, further confirming the lack of association between secondary sex ratio (boys to girls at birth) and time to pregnancy. On this point, we are confident the authors are correct. However, their hypothesis that the sex ratio could be a marker of adverse effects on the male reproductive system is less certain. They suggest that a slight decline over time in the secondary sex ratio could represent deterioration in male reproductive health. But does it?

The sex ratio at birth is a prevalence measure. Firstly, it reflects the relative number and fertilising capacity of sperm bearing X and Y chromosomes that reach the ovum in the female genital tract, and secondly it reflects the relative survival of male and female conceptuses in early pregnancy. In human semen, the number of spermatozoa with X and Y chromosomes is equal. However, from the time that pregnancy is clinically recognised (around six weeks after last menstrual period), males are the more prevalent. What happens in those early weeks to create this male excess? It is not known whether this results from a higher fertilising capability of spermatozoa bearing Y chromosomes, or a preferential loss of female fetuses during fertilisation, implantation, and early embryogenesis.[5] It seems unlikely that males are the better survivors during this period, given the excess mortality of males throughout the rest of pregnancy (and for a long time thereafter).

Added to this mystery are the few factors that are known to be associated with sex ratio. The proportion of males decreases with increasing parental age, and it is higher in white people than in black people.[6] Studies of inter-racial marriages indicate that the race difference is determined by paternal factors,[5] but the mechanisms are unknown.

Changes have occurred in the secondary sex ratio over time, although they are very small. During the past 60 years, the proportion of male babies decreased from 51.54% to 51.38% in Europe (a shift of fewer than two babies in 10 000 from male to female).[7] In the United States the sex ratio increased between 1959 and 1971 (from 51.17% to 51.30% males) and then decreased to 51.14% in 2002.[6]

One of the most quoted areas of research on sex ratio is the effects of toxic exposures.[8] However, the evidence that reproductive toxicants interfere with the sex ratio is weak or circumstantial, and the mechanisms involved are conjectural.[9] For example, DBCP (1,2-dibromo-3-chloropropane) is a powerful male reproductive toxicant that can cause complete sterility. DBCP is regarded as a prime example of a toxicant that changes the secondary sex ratio. To our knowledge, however, this claim is based on one small study.[10] Similarly, while positive studies may have been reported, there is no compelling or consistent evidence that well established reproductive hazards such as tobacco smoke, ionising radiation, or inorganic lead have any impact on the sex ratio of offspring.[11]

Why then does sex ratio continue to attract so much scientific attention? One reason may be

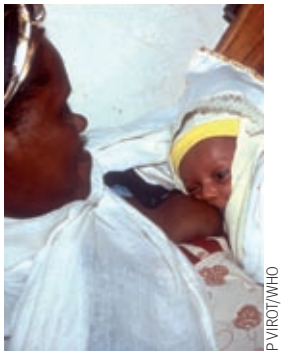
that it is so easy to measure. Literally thousands of studies include information on sex of offspring. With so many opportunities for analysing data, it is hardly surprising that striking findings emerge. When they do, imaginative researchers have no trouble constructing plausible biological mechanisms to explain their findings. Such hypotheses often assume a life of their own (as with sperm bearing Y chromosomes being faster swimmers), even as the original observations fail for lack of confirmation.

This is not to say that the secondary sex ratio is of no interest. One of the most important reproductive trends of this new century may be the rising secondary sex ratio in China, where today 117 boys are born for every 100 girls.[12] This enormous deficit of females has disturbing implications for future societal stresses in China—and thus for the rest of the world. But in terms of the sex ratio being a barometer of male reproductive health, we remain doubtful. The sex ratio is an endpoint particularly vulnerable both to false positive reports and fanciful interpretation. Positive findings should be treated with scepticism.

1 Smits LJ, de Bie RA, Essed GG, van den Brandt PA. Time to pregnancy and sex of offspring: cohort study. *BMJ* 2005;331:1437-8.
2 Olsen J, Weijin Z, Jin LZ. Time to pregnancy and sex ratio of offspring. Electronic response to Smits LJ, et al. Time to pregnancy and sex of offspring: cohort study. *BMJ* 2005. www.bmj.com/cgi/eletters/331/7530/1437#124413.
3 Grant VJ. Entrenched misinformation about X- and Y-sperm. Electronic response to Smits LJ, et al. Time to pregnancy and sex of offspring: cohort study. *BMJ* 2006. www.bmj.com/cgi/eletters/331/7530/1437#130012.
4 Joffe M, Bennett J, Best N, Jensen TK. Sex ratio and time to pregnancy: analysis of four large European population surveys. *BMJ* 2007 doi: 10.1136/bmj.39097.508426.BE.
5 Boklage CE. The epigenetic environment: secondary sex ratio depends on differential survival in embryogenesis. *Hum Reprod* 2005;20:583-7.
6 Mathews TJ, Hamilton BE. Trend analysis of the sex ratio at birth in the United States. *Natl Vital Stat Rep* 2005;53:1-17.
7 Martuzzi M, Di Tanno ND, Bertollini R. Declining trends of male proportion at birth in Europe. *Arch Environ Health* 2001;56:358-64.
8 Weijin Z, Olsen J. Offspring sex ratio as an indicator of reproductive hazards. *Occup Environ Med* 1996;53:503-4.
9 Trasler J. Paternal exposures: altered sex ratios. *Teratology* 2000;62:77-8.
10 Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. *J Occup Environ Med* 1995;37:1287-92.
11 Heron J, Ness A. Lack of association between smoking behavior and the sex ratio of offspring in the Avon longitudinal study of parents and children. *Fertil Steril* 2004;81:700-2.
12 Wu Z, Viisainen K, Hemminki E. Determinants of high sex ratio among newborns: a cohort study from rural Anhui province, China. *Reprod Health Matters* 2006;14:172-80.

Infant feeding and HIV

Avoiding transmission is not enough



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Recently, the World Health Organization updated its recommendations of 2000[1] on infant feeding in the context of HIV.[2] At that time, data had just been published quantifying the risk of infection through breast feeding so avoiding breast feeding was acknowledged as the only effective way of avoiding transmission.[3] WHO had also just published a meta-analysis of the mortality risks of not breast feeding, but in non-HIV infected populations.[4] Considerations of these data resulted in the statement that, "When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended."[1] Since the 2000 recommendations, the main emphasis of most national programmes aimed at preventing mother to child transmission of HIV has been to avert transmission of HIV in young infants.

The most difficult challenge has been how to make breast feeding safer in communities with a high prevalence of HIV where breast feeding is the traditional mode of feeding. Remarkably, the dilemma of infant feeding and HIV has split scientific communities and programme managers into opposing camps. Even with the risk of HIV transmission, some maintain that breast feeding may still be the best option for many mothers infected with HIV because of its anti-infective and nutritional advantages.[5-7] Others promote commercial infant formula, arguing that the risks of diarrhoea and malnutrition associated with formula feeding are lower in most urban communities, or that the risks of not breast feeding may not be as great for infants born to mothers infected with HIV who, to prevent transmission, choose to give formula milk from birth; it has been suggested that this active decision making and motivation may result in safer preparation and use of formula milk.[8]

In South Africa, formula feeding was reported as a successful intervention with minimal morbidity in an urban transmission prevention programme.[9] However, this cross sectional study of just 113 infants recorded outcomes only in infants who were still being brought back to the clinics, and data from infants who had already died or had experienced serious morbidity would not have been reported. Recently, two reports have been published from Botswana[10 11] that, together with a compelling body of evidence from the literature in children without HIV,[4 12] emphasise that child survival must be seen as the greater goal; greater even than "just" avoiding HIV infection.

The first is a randomised trial evaluating whether giving zidovudine to infants exposed to HIV while breast feeding resulted in more infants surviving and not being infected with HIV than giving formula milk to infants from birth.[10] It found no significant difference in HIV-free survival rates of infants at 18 months; any gains from reducing transmission by giving formula milk were lost through increased mortality from diarrhoea and malnutrition. At 7 months the infants who were formula fed from birth had almost twice the mortality risk of those who were breast fed (9.3% *v* 4.9%; P=0.003). Importantly, the data suggested that giving antiretroviral drugs to the mother may reduce transmission of HIV through breast feeding,

whereas giving zidovudine to the infant alone seems to have little impact on transmission.

The second report, an investigation conducted by Centers for Disease Control, followed an outbreak of severe diarrhoea and malnutrition across the entire country that, in the first three months of 2006, accounted for 22 470 cases and 470 related deaths in children under 5 years.[11] In the same months in 2004 and 2005, there were 8478 and 9166 cases of diarrhoea and 24 and 21 related deaths, respectively. In children admitted with severe diarrhoea, not breast feeding was the biggest risk factor (adjusted odds ratio 50.0; 95% confidence interval 4.5 to 100); this was in spite of 97% mothers having access to piped water sources and most having been part of the HIV transmission prevention programme and therefore counselled on safe replacement feeding practices.

Should we be surprised by these data? In the original randomised trial in Kenya when the risks of postnatal HIV transmission in an African setting were first quantified,[3] the risk of mortality associated with formula feeding in the first 6 months of life were similar to those described in the randomised trial in Botswana. By 18 months, however, and in contrast to the recent Botswana study, infants who had been randomised to formula feeding had better HIV-free survival. The mothers in this study also had access to safe water, electricity, and medical care and formula milk was supplied by the study (that is, all the effective conditions deemed necessary in the 2000 WHO recommendations). The irony of these reports is that Botswana arguably has the best primary health infrastructure and provision of water and sanitation in southern Africa. The national HIV transmission prevention programme was the first to promote formula milk as the default feeding option for mothers infected with HIV and it seemed to be successful. As alarming as the report of epidemic diarrhoea and ensuing deaths might be, we should be more concerned about possible longstanding unrecognised mortality related to mothers making inappropriate choices of infant feeding practices when their household circumstances cannot safely support those practices and infants are thereby at high risk of diarrhoeal illness, malnutrition, and death.

The updated WHO report and recommendations,[2] while generally supportive of the 2000 recommendations,[1] provide greater insight and nuance to the complexity of implementing any theoretical approach in programmes. They acknowledge that exclusive breast feeding has a twofold to fourfold lower risk of transmission than mixed feeding.[13 14] They recommend that in the absence of safe water, hygiene, and community acceptance exclusive breast feeding should be promoted until the infant is 6 months old rather than just during the first few months of life. The continued risks of serious morbidity and mortality in infants if breast feeding is stopped early at around six months was highlighted stressing the need for continued contact and counselling with mothers during the first months of the infant's life to help guide her decisions about feeding practices after 6 months. Most important, perhaps, was the acknowledgement that the health systems in which transmission prevention programmes are implemented must be able to cope with the diarrhoeal illnesses and malnutrition that are so frequently the consequence of incorrect use of commercial infant formula.[2]

There is no doubt that breast milk can transmit HIV or that an infant's chances of survival when living in a poor or rural community are greatly decreased by not breast feeding. The challenge is how health systems can, at scale, help individual women, whether infected with HIV or not, appreciate the inherent risks and opportunities of their environment and make good decisions about how to feed their infants. For scientists, the challenge is to study and understand the evidence and not simply follow their hearts and possible prejudices in this crucial component of child survival.

1 WHO. *New data on the prevention of mother-to-child transmission of HIV and their policy implications: conclusions and recommendations*. WHO technical consultation on behalf of the UNFPA/UNICEF/WHO/UNAIDS inter-agency task team on mother-to-child transmission of HIV. WHO/RHR/01.28ed. Geneva: WHO, 2001. www.who.int/reproductive-health/publications/new_data_prevention_mtct_hiv/index.html.

2 WHO. Consensus statement. *WHO HIV and infant feeding technical consultation held on behalf of the inter-agency task team (IATT) on prevention of HIV infections in pregnant women, mothers and their infants. Geneva, October 25-27, 2006*. www.who.int/child-adolescent-health/New_Publications/NUTRITION/consensus_statement.pdf.

3 Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, et al. Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA* 2000;283:1167-74.

4 WHO Collaborative Team. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. *Lancet* 2000;355:451-5.

5 Piwoz EG, Ross JS. Use of population-specific infant mortality rates to inform policy decisions regarding HIV and infant feeding. *J Nutr* 2005;135:1113-9.

6 Ross JS, Piwoz EG, Habicht JP. Is breastfeeding best for HIV-positive mothers? *AIDS* 2004;18:363.

7 UNICEF, USAID. HIV and infant feeding: a compilation of programmatic evidence. QAP, University Research Co, LLC (URC), 2004. www.qaproject.org/strat/sourcedoc.htm.

8 Brahmbhatt H, Gray RH. Child mortality associated with reasons for non-breastfeeding and weaning: is breastfeeding best for HIV-positive mothers? *AIDS* 2003;17:879-85.

9 Hilderbrand K, Goemaere E, Coetzee D. The prevention of mother-to-child HIV transmission programme and infant feeding practices. *S Afr Med J* 2003;93:779-81.

10 Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, et al. Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi study. *JAMA* 2006;296:794-805.

11 Creek T, Luo C, Quick T. HIV-exposed children highly affected by deadly outbreak of diarrhea and severe acute malnutrition—Botswana, 2006. The 2006 HIV/AIDS implementers meeting of the president's emergency plan for AIDS relief, Durban, South Africa, Late Breaker Abstract 1, 2006. www.blsmeetings.net/implementhiv2006/TracyCreek_files/frame.htm.

12 Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, et al. Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bull World Health Organ* 2005;83:418-26.

13 Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS* 2005;19:699-708.

14 Coovadia H, Rollins N, Bland R, Little K, Coutsoudis A, Bennish ML, et al. Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding: the first six months of life. *Lancet* 2007 (in press).