perspective and doesn't fulfil requirements for equity at national or international levels.

Introducing user charges is likely to be inequitable as well as adversely affecting adherence.[18 19] Many families will already be living in poverty as a result of a reduction in income or paying for AIDS care. Providing free access to antiretroviral drugs based on rights and not ability to pay,[19] as occurs in the Senegal national programme, will be most equitable, will resolve dilemmas over the treatment of migrants, and will also reduce migration to obtain antiretroviral drugs.

Conclusions

The 3 by 5 initiative faces important challenges in meeting the desperate need for antiretroviral drugs in many developing countries,. Constructive dialogue between stakeholders with different agendas, including healthcare workers, public health managers, community and faith based organisations, and people with AIDS, will be crucial if the initiative is to succeed. The prevailing social strategies must be considered carefully when setting up programmes and working relationships, in order to capitalise on and not undermine the existing social order. In an interview in Bangkok, the executive director of UNAIDS noted that "antiretroviral therapy is still a rare commodity, and it will be for some time. The result of that is always higher price, and also higher price in terms of power. Who has access to it, and who comes first: it's a terrible issue."[w20] Without addressing this and the other issues we have raised, the 3 by 5 initiative may fall short of its goals.

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Summary points

- The 3 by 5 initiative aims to deliver antiretroviral drugs to three million people with HIV infection in developing countries by 2005
- To succeed, the initiative must develop a chronic disease model of care through a strengthened public health infrastructure
- Cooperation is needed with existing essential programmes to manage scarce health staff
- The influence of stigma requires monitoring
- Access to treatment must be based on rights and not ability to pay

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Natural killer cells, miscarriage, and infertility

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Enthusiasm for new treatments aimed at natural killer cells in women with reproductive failure is unfortunately not backed up by the science

Natural killer (NK) cells have an important role in the early responses to viral infections and have also been linked with failure of pregnancy. Recent reports in the media and the internet have exposed women to a baffling array of conflicting information about tests for NK cells and "cures" for infertility and miscarriage. These are based on the premise that malfunction of NK cells causes these conditions. Increasingly, clinics are offering blood tests to measure the number and activity of circulating NK cells. As a result of these investigations, many women are offered treatments such as steroids, intravenous immunoglobulins, and tumour necrosis factor α blocking agents. The scientific rationale for these tests and treatments, however, is not supported by our current knowledge of the function of uterine NK cells.

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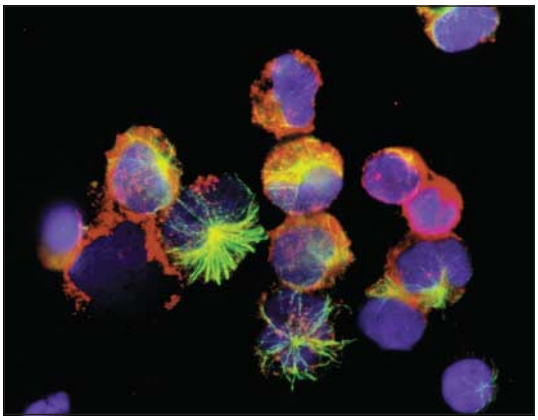
Uterine natural killer cells

Natural killer cells (identified by the surface marker CD56) are the dominant type of maternal immune cell populating the uterine mucosa during formation of the placenta.[1] These uterine NK cells are also present in the endometrium of non-pregnant women, when they are under the control of ovarian hormones, cycling together with the glandular and stromal compartments. After ovulation, uterine NK cells proliferate vigorously so that by the late secretory phase they account for at least 30% of the endometrial stroma.

Uterine NK cells persist in the early decidua and accumulate in large numbers at the implantation site. Here they are in close contact with the invading placental trophoblast cells, which transform the spiral arteries into high conductance vessels. This transformation is essential to ensure a normal blood supply to the fetus and placenta throughout pregnancy. Of central importance is that uterine NK cells are phenotypically and functionally different from NK cells in peripheral blood and should be regarded as a separate lymphoid subset.

The presence of an apparently unique type of lymphocyte in the uterus at implantation and during early placentation is intriguing. However, despite much speculation, the function of uterine NK cells is completely unknown. They may affect the cycling endometrium by controlling vascular function through secretion of angiogenic growth factors. In this way they may be crucial in the decision to switch from endometrial breakdown (menstruation) to decidualisation in pregnancy.[2] More attention has been directed at their possible role in regulating the fetal supply line by modulating the structural adaptation of the uterine spiral arteries. This is achieved by invasion of the maternal decidua and adjacent myometrium by invasive fetal trophoblast cells. Trophoblast invasion is defective in intrauterine growth restriction, pre-eclampsia, and miscarriage.[3] How NK cells recognise trophoblast and the outcome of this recognition are under investigation. Recently, the NK cell receptors that can bind to trophoblast MHC class I molecules have been identified, and this has opened up new ways to study the function of uterine NK cells.[4 5]

At present, despite their compelling name, there is no evidence that uterine NK cells kill placental trophoblast cells. Instead, they probably have an essential, beneficial effect on trophoblast by secreting cytokines that alter the depth of placental invasion. Natural killer cells acquired their name as a result of the initial test used to identify them in vitro. Unlike T lymphocytes, NK cells are able to spontaneously kill cells in a non-MHC restricted manner. Regrettably, this is a misleading name in reproduction, and the powerful image of maternal cells attacking the fetus is emotive and easily exploited.



NANCY KEDERSHA/SPL

Immunofluorescent light micrograph of human natural killer cells

Testing of peripheral blood NK cells

Based on the assumed similarities between NK cells in blood and uterine NK cells, it has become increasingly common to examine peripheral blood NK cells in women with infertility and recurrent miscarriage. These tests are based on the speculation that women with recurrent miscarriage and infertility have abnormalities in uterine NK cell function, and it has been implied that these are discernible from analysis of NK cells in blood.[6 7] This approach has several problems. Firstly, as mentioned above, uterine NK cells are different from those in peripheral blood. Examination of peripheral blood NK cells will not tell us what is happening in the uterus. This is akin to estimating the number and activity of black cabs in Trafalgar Square by analysing red mini-cabs circulating on the M25.

Secondly, the percentage of CD56+ NK cells in peripheral blood in normal healthy individuals varies from 5% to 29%.[8] Despite this, a finding of more than 12% NK cells in women with infertility or miscarriage has been arbitrarily defined as abnormally raised and used as an indication for treatment.[9] The percentage of NK cells in blood can be affected by many factors including sex, ethnicity, stress, and age, but there is no indication that concentrations in the upper end of the normal range are ever harmful.

Thirdly, NK activity is measured by a range of assays and the results will vary in different laboratories. The most commonly used in vitro assay is cytotoxicity, which may not have much relevance to NK function in vivo.[10] Certainly, in viral infection, NK cells function mainly by producing cytokines. Furthermore, uterine NK cells have much lower cytolytic activity than blood NK cells. Thus, no clinically relevant information is gained from studying either the percentage or cytotoxicity of blood NK cells in women with pregnancy failure.

Uterine NK cells in pregnancy failure

Attempts have also been made to compare the number of NK cells in the non-pregnant endometrium of women with recurrent miscarriage or infertility with that in normal controls.[11 12] These studies are based on the doubtful premise that the unknown roles of NK cells actually relate to the numbers present. Normally, numbers of uterine NK cells change rapidly after ovulation, and quantification must be carefully correlated with the surge in luteinising hormone. Furthermore, the density of NK cells throughout the mucosa is not constant, so all samples should be analysed at the same depth beneath the surface epithelium. It is not surprising that the results are conflicting. Regrettably, an anecdotal case of a woman with "excessive natural killer cells" has been reported on BBC Radio 4's *Woman's Hour* (22 Jan 2004) and several national newspapers.[13] The so called excessive

Summary points

- Natural killer (NK) cells are the main type of lymphocyte in the uterine mucosa at implantation and during early pregnancy
- Uterine NK cells are different from those circulating in peripheral blood
- The function of uterine NK cells in pregnancy is unknown
- Tests to measure NK cells in peripheral blood give no useful information on uterine NK cells
- Use of powerful therapies to reduce levels of NK cells in women with infertility or recurrent miscarriage is unjustified and is associated with known side effects to mother and fetus

numbers and activity of NK cells, which are well within the range for healthy women, are used as the reason for treatment.

Treatments for miscarriage and infertility

Infertile women and those with recurrent miscarriages are being given treatments such as steroids, intravenous immunoglobulin, and tumour necrosis factor-α blocking drugs with the questionable aim of suppressing NK cells. Recent high profile radio and press reports have featured a UK trial of steroids in recurrent miscarriage that has not been published but claims a success rate of about 85% (*Woman's Hour,* 29 Jan 2004).[14] How this study was controlled is uncertain, but it is important to bear in mind the placebo effect and the well documented success achieved with such patients simply using care and reassurance.[15] Neither steroids nor the other treatments being offered to women with "raised" levels of NK cells in blood are licensed for use in reproductive medicine, and all these treatments are associated with known risks to mother and fetus. The treatments are offered despite recent guidelines from the Royal College of Obstetricians and Gynaecologists, a Cochrane review, and a meta-analysis all concluding that there is no evidence to show they are beneficial.[16–18] The situation is reminiscent of the publicity and controversy surrounding paternal leucocyte immunisation as a treatment for recurrent miscarriage in the 1980s. After much flurry and expense, this treatment has now been banned by the US Food and Drug Administration.[19]

Understanding the function of uterine NK cells is certainly a major challenge in human reproduction. However, until more is known about their role in normal pregnancy, there is no evidence of any benefit in offering NK cell testing to women with recurrent miscarriage or infertility. Of course, women with these distressing conditions will be disappointed. In the technological medicine of today, patient expectations are high and a lack of a diagnosis and treatment is hard to accept. The danger posed by internet sources, the popular press, and radio highlighting idiosyncratic personal practices of a few physicians should not be underestimated. This unfortunate group of women are particularly vulnerable to financial exploitation, and of being exposed to powerful treatments that have, as yet, no rational scientific basis.

Contributors and sources: AM is a leading international authority on the role of uterine natural killer cells in reproduction, PB is on the Human Fertilisation and Embryology Authority and is a leading fertility expert, and LR is an expert on recurrent miscarriage and runs the largest miscarriage clinic in Europe. AM provided the scientific basis and wrote the paper. LR and PB provided clinical and ethical advice. AM is the guarantor.

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Endpiece

Not enough

Clarity and certainty are essential to surgeons in training, at least until they discover that clarity is not enough and certainty does not exist.

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