EDITOR,—Nicholas J Wald and colleagues have provided valuable data concerning the introduction of maternal screening for Down's syndrome using three serum markers.¹ The benefits of serum screening as an alternative to a diagnostic test in mothers over 40 is still debated, and some argue that this group should still be offered a diagnostic test, with the possible benefit of a first trimester diagnosis, if available.

Wald and colleagues showed a false positive rate (number of mothers requiring amniocentesis) of 4.9% in women under 37 and 22% in those aged 37 or over.¹ This increase in the number of false positives obviously reflects the effect of maternal age on the incidence of Down's syndrome.

A similar screening programme was introduced in Chester six months ago with a risk of 1 in 250 or greater denoting a positive result. A total of 1820 mothers have been screened to date, with an overall false positive rate of 4.8% (88/1817) after correction for gestational age. The false positive rate in women over 37 was 34% (21/61), and in women over 40 was 69% (9/13). Overall screening detected three chromosomal abnormalities; two in women over 37 and one in women over 40.

The number of mothers screened in our population is small, which makes interpretation of the data difficult, but these results suggest that a diagnostic test may be more appropriate for women over 40. Further analysis of Wald and colleagues' data would be interesting for comparison.

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1 Wald NJ, Kennard A, Densen JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. *BMJ* 1992;305:391-4. (15 August.)

EDITOR,—In the paper by Nicholas J Wald and colleagues on antenatal maternal screening for Down's syndrome the term incidence is incorrectly used (in the summary table).¹

Down's syndrome occurs at the time of fertilisation of the ovum and incidence may be used only if it is known how many fertilised ova have trisomy 21. Between the moment of fertilisation and the performance of the screening test spontaneous abortion may occur, and it is well recognised that there is a disproportionately greater number of chromosome anomalies among spontaneous abortions. At the time of screening there may already have been a selective loss of affected fetuses. Therefore, what is being measured is prevalence of Down's syndrome at the time of screening. The incidence cannot be determined unless it is known how many affected fetuses were spontaneously aborted before screening was performed.

There is an arithmetic relationship between incidence and prevalence and, even if incidence remained constant, the prevalence at screening could vary considerably owing to any change in a variety of factors that affect the rate of spontaneous abortion.

As this principle applies to all congenital anomalies, in the current state of knowledge it is incorrect to refer to the incidence of any congenital anomaly. The differentiation between incidence and prevalence is not merely an academic exercise. If the aetiology of a disease is under consideration, it is essential to examine incidence. If prevalence is examined, it may be affected by either the incidence or the duration of the disease.

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1 Wald NJ, Kennard A, Densen JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: results of a demonstration project. *BMJ* 1992;305:391-4. (15 August.)

EDITOR,—Our paper¹ and two other demonstration projects just published^{2,3} show that serum screening for Down's syndrome using the triple test is practical and has produced results consistent with previous estimates of screening performance. An important issue lost in some of the correspondents' comments is that serum screening detects twice as many affected pregnancies as age screening for the same false positive rate. If screening for Down's syndrome using maternal age is acceptable then so is serum screening since it simply achieves the same result more effectively.

We deal with the correspondents' points under nine headings.

The performance of the test. With only 25 affected pregnancies, an estimate of the detection rate is subject to considerable random error. We noted this in our paper, referring to the more reliable estimates of a 58% detection rate for a 5% false positive rate previously published.^{1,5} Combining the results of our demonstration project with those from the New England project² (38 000 screened women)² yields a detection rate of 54% and a false positive rate of 4%, close to that predicted. A demonstration project conducted in Tennessee among women aged less than 35 years detected four out of seven affected pregnancies with a false positive rate of 3%.³ Caution is needed in interpreting detection and false positive rates from individual programmes because of statistical variation arising from small numbers and the effect of local variation in the use of ultrasonography, repeat testing, and choice of risk cut off levels. Citing detection rates, as Macri and Clarke do, without corresponding false positive rates is unhelpful.

Costs of screening. The estimates of costs in our paper are valid. They were directly incurred in providing the service—about £15 per woman screened, which is the current charge for the service organised through antenatal clinics. Included is the provision of information leaflets, seminars, and specialist and counselling support as required. Undoubtedly, we could improve in this area, and this aspect of screening must not be neglected.

The choice of screening markers. Spencer again says that free β human chorionic gonadotrophin is a better second trimester screening marker for Down's syndrome than intact human chorionic gonadotrophin.⁶ As we and others have said before,^{7,8} he may be correct, but the question remains open and it was not our aim to investigate alternative markers. We have also responded to comments on the use of unconjugated oestradiol before, and estimated the gain in performance using this marker—an increase in detection of 9% and 4% for a 5% false positive rate, respectively with and without the use of ultrasound to estimate gestational age.

The women who were not screened. There were seven pregnancies with Down's syndrome in the unscreened women. Their median age was 36 years and three had amniocentesis.

Miscarriage rate due to amniocentesis. We did not quote a miscarriage rate because this would not reveal the risk related to the procedure. The best evidence on the fetal loss rate comes from the randomised trial performed by Ann Tabor and her colleagues, indicating that the risk is about 1%.⁹

Confirmation of abnormality in the fetuses aborted. All aborted fetuses had the diagnosis of Down's syndrome confirmed by chromosome or pathological analysis, usually by both.

Effect of the age distribution of women on screening performance. This is small and, regardless of variation in the age distribution of women, serum screening will yield a higher detection rate for a given false positive rate than maternal age screening alone.

Limiting serum testing to younger women. The disadvantage of this approach is that it is less efficient and less equitable than serum screening

for all women. More amniocenteses would need to be performed for the same number of detected cases. About half of women aged 40 years and over would be offered an amniocentesis even though a serum test would have indicated a low risk, while almost all affected pregnancies (95%) in these older women would still be detected.

α Fetoprotein screening for spina bifida. This should not be abandoned. If ultrasound scanning is used routinely to estimate gestational age, about 85% of open spina bifida cases can be detected using an α fetoprotein cut off level of 2.5 multiples of the median, with only about 2% of unaffected singleton pregnancies having α fetoprotein values this high.² It would need to be shown that screening for spina bifida using routine ultrasound scanning in antenatal clinics had a performance at least as good as this before a change in α fetoprotein screening was warranted.

There is no doubt that serum screening using the triple test is more effective than screening based on maternal age alone and can be readily applied in practice. Some of your correspondents' comments, if interpreted uncritically, may delay women's access to a screening service. It is important that this is not allowed to happen.

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1 Wald NJ, Kennard A, Densen JW, Cuckle HS, Chard T, Butler L. Antenatal maternal serum screening for Down's syndrome: Results of a demonstration project. *BMJ* 1992;305:391-4. (15 August.)

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Assisted conception on NHS

EDITOR,—We work in an assisted conception unit that has been trying to provide in vitro fertilisation and other infertility treatments within the NHS since 1984, and we welcome David T Baird's rational appeal for more NHS funding for assisted conception.¹ We recently surveyed 13 large assisted conception units, of which 11 functioned within or closely associated with NHS or university departments of obstetrics and gynaecology. Only five of the units have been treating NHS patients, and three of these charge the patients a fee of between £350 and £900 per treatment cycle (exclusive of drugs). Several units were hoping to

obtain health authority funding in the current financial year, charging the authority between £530 and £900 per cycle. One of the private units was negotiating to obtain health authority contracts for £1500 per cycle (excluding drugs).

Our NHS trust has elected to exclude in vitro fertilisation from block contracts, which are held with 50 or so districts, and it is encouraging that about half of those have so far agreed to pay for this treatment on an extracontractual referral basis, but with a wide variety of "rationing" conditions. The charge for a cycle of in vitro fertilisation, including drugs, is roughly £1200, and for tubal surgery as an extracontractual referral the charge is £2639 (but most districts have not excluded tubal surgery from their block contracts).

To help purchasing authorities make rational choices they need to be reminded of expected rates of successful pregnancy from these treatments and to be aware that tubal surgery produces extremely variable success rates (5%² to 36%³), depending on the severity of the tubal disease, age of the patient, and skill in the surgical technique. The table gives the comparative costs of the two treatments depending on the pregnancy rate.

Comparative costs per baby of in vitro fertilisation (IVF) and tubal surgery with different pregnancy rates

Procedure	Cost (£)	Live birth rate (%)	Cost per baby (£)
Tubal surgery	2639	30	8 790
Tubal surgery	2639	5	52 780
IVF, 4 cycles (including drugs)	4800	60 (cumulative)	8 000

Gynaecologists must be highly selective in their approach to tubal surgery if they are to ensure that resources which could be directed to assisted conception more effectively are not wasted on tubal surgery with a poor prognosis.

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- 1 Baird DT. Assisted conception on the NHS? *BMJ* 1992;305:204-5. (25 July.)
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EDITOR,—David T Baird's editorial on assisted conception raises the issue of funding for comprehensive infertility services in the NHS.¹ As the director of one of the few NHS units in the United Kingdom, I agree that appropriate resources are urgently needed to support such activities. My experience since the changes in the NHS has been that the decisions relating to funding of assisted conception have now been placed in the hands of the district purchasers, who, unlike the suffering infertile couples, do not see infertility as a priority.

Purchasers are adopting various strategies: many are ignoring extracontractual requests; a few are acknowledging extracontractual requests but making no firm decisions; a minority are refusing outright; and an extreme minority are agreeing to a limited number each year (that is, rationing in their own district). Because purchasers are funding so few extracontractual requests despite the demand from patients (>250 on our waiting list) Guy's Hospital can no longer support a programme of assisted conception on the NHS. Other units associated with the NHS have survived and prospered by becoming private. Reluctantly, we may have to do this too.

The broader issue that needs to be addressed

publicly is that of rationing health services. Rationing has always occurred, but the purchaser-private split highlights the problem. Currently, a small group or perhaps only one public health doctor or manager is making decisions on behalf of infertile couples. Interestingly, we have noticed that the more supportive purchasers have been those with women participating in the decision. Such rationing behind closed doors is against the principle of patients having the power to choose and money following patients. Public debate on this is urgently required.

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- 1 Baird DT. Assisted conception on the NHS? *BMJ* 1992;305:204-5. (25 July.)

EDITOR,—Trevor Sheldon and colleagues present surprisingly negative comments on the effectiveness of infertility treatment,¹ particularly in view of the encouraging messages fronting their review in the most recent issue of *Effective Health Care*.² They comment sweepingly about all infertility medicine, though it covers a wide range of distinct disorders, which need specific consideration. Proper balance is required.

A critical review of infertility treatment has been published elsewhere.³ Controlled studies have shown a lack of therapeutic effectiveness of, for example, hormones or surgical ablation in minor endometriosis and of hormones, artificial insemination, and (generally) microinjection techniques in sperm disorders. Randomised controlled studies are lacking in other conditions, but prospective time specific studies without treatment have shown severe subfertility associated with, for example, infective tubal damage, severe endometriosis, amenorrhoea, and prolonged unexplained infertility. In all those conditions natural conception rates are around 1% each cycle and amount to 10-30% over two years.

Prospective studies of treatments can therefore be reasonably judged by comparison with such well defined, severely reduced rates of natural conception. Furthermore, they can be assessed by comparison with expectations of normal fertile couples—that is, pregnancy rates averaging 20-25% each cycle and amounting to 90-95% after one to two years (or equivalent number of cycles of treatment).

It is now clear that hormonal treatment of amenorrhoea is fully effective; surgery of even the highest quality offers only moderate success in a select minority of cases of tubal damage; and in vitro fertilisation to bypass tubal damage offers success rates approaching normal, and the same is true of other assisted conception methods like gamete intrafallopian transfer, which can also be used in endometriosis and prolonged unexplained infertility.

Important differences between natural and assisted conception methods are that assisted conception risks multiple pregnancy—but that is now strictly limited in Britain—and do not involve the same time span. In general, assisted conception is undertaken at most every two cycles and often at longer intervals depending on resources (both NHS and personal).

The fact that such clinical treatments may be undertaken only infrequently, seemingly reducing their effectiveness in terms of time specific pregnancy rates, is not a real criticism of their effectiveness. It is reasonable personal and clinical philosophy for a couple to have in vitro fertilisation say two to four times in a year, which each time offers about a 25% chance of success compared with 3-4% by natural means during the intervals.

What is needed is a general raising of standards

of infertility practice to what is now undoubtedly achievable in all competent centres.

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- 1 Sheldon TA, Song F, Freemantle N. Assisted conception on the NHS. *BMJ* 1992;305:521. (29 August.)
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Heterosexual AIDS epidemic

EDITOR,—Although the AIDS epidemic continues to grow and people are being infected worldwide, the medical literature trails behind. Almost half of the one million adults infected so far this year have been women. The gap in transmission rates in Britain and the rest of Europe between heterosexual and homosexual has narrowed. But information about the disease is still male dominated. At risk groups are still being highlighted, rather than high risk behaviour.

One general practitioner journal recently carried a whole symposium on HIV infection and AIDS and did not mention women once.¹ Another journal reviewed presentation and treatment of fungal infections in HIV without mentioning the vagina.² A recent atlas of AIDS showed out of 153 case presentations, only two presentations of women.³ The list is endless.

Unless we challenge this women will continue to be diagnosed later, be given second class treatment, and forgotten when it comes to work on prevention.

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Low serum cholesterol and violent death

EDITOR,—Gunnar Lindberg and colleagues found that in men low cholesterol concentrations were associated with a higher rate of suicide in the subsequent six years.¹ Similarly, when Muldoon *et al* reviewed six trials of lowering serum cholesterol concentration by drug or diet they found a significant increase in deaths due to suicides and violence.² It seems possible that if a low cholesterol concentration predisposes a few to the extreme act of suicide then others are likely to experience less severe depression. The questions posed by these data may well be best investigated by using a more subtle measure than the rate of suicide. We reanalysed data on serum cholesterol concentration and mental health in a group of subjects.

Serum cholesterol concentrations in 130 men and 155 women (mean age 20.5 years) who had fasted overnight were related to scores on the general health questionnaire, which is designed to screen for psychiatric problems. The average cholesterol concentration was 4.03 (SD 0.73) mmol/l in the men and 4.47 (0.99) mmol/l in the women. The sample was grouped in terms of cholesterol values, and the scores on the general health questionnaire were analysed with analysis of variance; the interaction of sex and cholesterol concentration was significant ($F_{2,268}=3.50$, $p<0.03$). The table shows that there was no general relation between cholesterol concentrations