# 1

# Down's syndrome epidemiology and biochemical screening

ERNEST B. HOOK

One may consider at least four major questions about the epidemiology of Down's syndrome that are pertinent directly or indirectly to biochemical screening and prevention.

(1) What is the impact of this disorder upon society, i.e. why *should* society screen?
(2) What variables are associated with Down's syndrome that one may consider in adjusting results from screening?
(3) What are the implications for policy issues?
(4) What are the possibilities for future primary prevention?

## Impact

Variation in the use of selective abortion of affected conceptuses and fertility among older mothers make it difficult to quantify the global impact of Down's syndrome, but clearly it makes a major contribution to the proportion of mental retardation. Earlier European data, in which older women ($\geq$35 years) probably contributed well over 10% of livebirths to the population and prenatal diagnosis was not in use, suggest that Down's syndrome contributed about 10% of those with IQs under 20; about a third of those with IQs 20–49; and a smaller but variable proportion, about 3%, of those with moderate retardation but with IQs 50 or over. Other studies are compatible with even higher proportions among those with IQs under 50, about a third of the total. (References to earlier literature appear in Hook, 1985a.)

In recent studies, derived from populations in which there are proportionally fewer older women having children ($<$10%), the proportion of those with retardation diagnosed as Down's syndrome has been lower.

These suggest a proportion of about 10% among those 'mentally handicapped' (e.g. Rasmussen *et al.*, 1982 cited by Webb *et al.*, 1987; Dereymaeker *et al.*, 1988). In areas in which relative fertility of older women is still high, however, the proportion is probably close to that seen earlier in European populations. For example, a study in Taiwan notes 18% Down's syndrome (Li *et al.*, 1988) among retardates. A recent study in Malaysia reports 32% of Down's syndrome in a group of retardates (Noor *et al.*, 1987) and published data for 1986–7 suggest 12% of mothers aged 35 years or over are affected (Boo *et al.*, 1989). (See also below.)

Mental retardation is not the only consequence of this condition. The increased frequency of other malformations, leukemia, etc. also puts a disproportionate burden on medical delivery systems. About 50% of these individuals have congenital heart defects (Fabia and Drolette, 1970), and about 12% of all livebirths with a congenital heart defect have a cytogenetic abnormality, about 75% of these being Down's syndrome (Ferencz *et al.*, 1987). With medical advances and social changes, these individuals receive more intensive and effective medical and surgical therapy in many jurisdictions, prolonging life and changing the life-span (e.g. Fabia and Drolette, 1970; Jones, 1979; Baird and Sadovnick, 1987, 1988, 1989). Data on differences in these trends appear in Mastroiacovo (1985); Malone (1988); Bell *et al.* (1989); Mastroiacovo *et al.* (1990). Despite the diminishing prevalence, either because of maternal age trends or because of more effective prenatal diagnosis, the economic impact of those affected who *are* born with the condition is likely to increase.

One economist estimated the excess economic cost to society of each Down's syndrome child over and above that of a normal child at $144 000 US (1985), discounted to the time of birth (Conley, 1985). This figure varies with factors such as health care practices and costs, mortality, special education, lost employment opportunity, and reimbursement, all of which obviously differ among jurisdictions and over time within areas. Assuming this figure is correct, in the USA, with a current expected livebirth prevalence rate of perhaps 1.2 to 1.3 per 1000 in the absence of prenatal diagnosis, society could justify (economically) spending up to $180 of such (1985) dollars for *each* pregnancy screened to detect *and prevent* a case. In the UK, with about the same background rate (Cuckle *et al.*, 1991), costs of £90 000 have been estimated (Gill *et al.*, 1987) implying a boundary of about £110. In areas such as Ireland (North or South) in which relative fertility is still high among older mothers (Radic, 1986; Dolk and Nevin, 1990) and the expected livebirth rate of Down's syndrome children is likely to be closer to 1.5 per 1000 (or even higher;

see, for example, Coffey and McCormick, 1977; Radic, 1986), even higher expenditure per pregnancy should be economically justified assuming the same baseline cost. This also assumes that a case diagnosed prenatally would be 'terminated', which is unlikely in a country without provision for selective abortion, let alone any abortion. Non-termination of prenatally diagnosed cases is an important but usually neglected factor in these analyses. Efforts targeted at older mothers would have even greater economic support, and one that increases with age and risk.

## Epidemiological issues related to screening

Apart from maternal serum analytes, selected abnormalities found in fetal imaging or fetal 47, +21 genetic material in maternal circulating blood, the only generally recognized *definitive* risk factors for a Down's syndrome livebirth are (elevated) maternal age, the birth of a previous affected individual, and the presence in one parent of a 47, +21 line or a structural rearrangement that will contribute a double dose of the responsible 21q region to a gamete. Individuals with the last two risk factors usually proceed immediately to prenatal cytogenetic diagnosis (at least in California), although biochemical screening results might diminish the need for that procedure in this group as well.

Age is the most ubiquitous risk factor for which adjustment of results from biochemical screening is required. The *relative* risks associated with observed values of maternal serum screening markers are multiplied by the baseline maternal age specific risk to derive an adjusted risk. (e.g Cuckle *et al.*, 1987; Palomaki and Haddow, 1987a; Tabor *et al.*, 1987; Miller *et al.*, 1991). But other biological and environmental factors have been proposed as associated with Down's syndrome. These could be used to adjust further the results from biochemical screening. Here I will address some of these but with particular focus on maternal age.

For historical reasons, women aged 35 years and over have been labeled 'high' risk and those under 35 years as 'low' risk for having a Down's syndrome infant. This goes back to the era when rates were calculated by 5-year intervals and a simple graph of rates imprinted on the viewer's eye an apparent quantum jump at 35 years (e.g. Penrose and Smith, 1966, p. 151, or Fig. 1.1.) The boundary is of course arbitrary (if we had six fingers, the boundary would have been 36). Moreover, when plotted by 1-year intervals, the rate changes gradually and continuously (Fig. 1.2). Nevertheless, the age 35 boundary point has been so imprinted in the

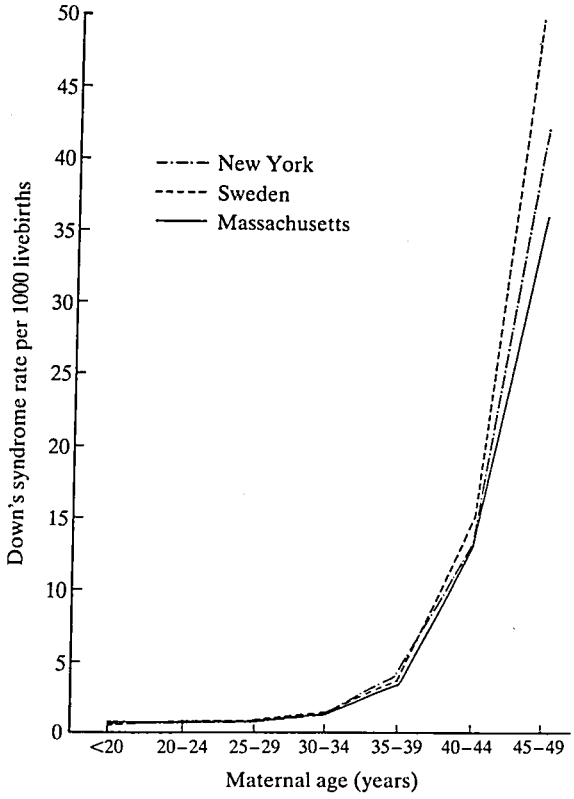


Fig. 1.1. Rates of Down's syndrome in three studies by 5-year maternal age intervals plotted on a linear scale. Note the abrupt change at 35–39 years.

medical mind that in many, but not all jurisdictions, it has been accepted as the established risk figure for provision of prenatal cytogenetic diagnosis. For example, in England, Scotland and Wales in 1991, of 97 Local Health Districts or Boards which did not perform serum screening (of a total of 200), two had a criterion of age $\geq$ 32 years, two a criterion of age $\geq$ 34 years, 49 at $\geq$35 years, 8 $\geq$ 36 years, 31 $\geq$ 37 years, and 5 $\geq$ 38 years (Wald *et al.*, 1992). The upper criteria are chosen, or may be chosen, to limit the impact upon diagnostic laboratories.

This has had a subtle, perhaps unappreciated, effect upon the significance of published risk figures by maternal age. For example, when I and others published risk figures by 1-year intervals, we viewed them as only rough guides to the magnitude of risk. Some disputes arose which focused on the major differences between, for example, rates in amniocentesis and in

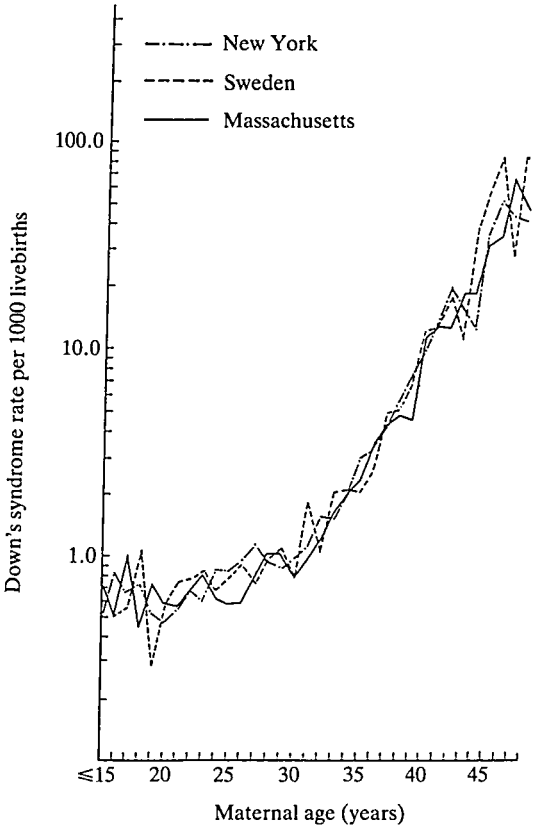


Fig. 1.2. Rates in the same population plotted by 1-year intervals on a log scale. Note no abrupt change at 35 years. (Reprinted with permission from Hook, 1982.)

livebirths (e.g. Ferguson-Smith, 1978; Hook, 1978). But all recognized that any point estimate will show variation.

Subsequent publications implied a variation in risk of Down's syndrome. But whether the rates at age 35 years were 1/350 or 1/400 or anywhere in this range did not affect the decision to have amniocentesis. The age not the risk figure provided the boundary. In the USA, for women under 35 years, the risk schedules were primarily of value because they gave women an indication of how close they came *relatively* to the risk at the generally agreed boundary.

Prenatal biochemical screening and 'at risk' projections derived from these results have changed the picture. Precise risk figures by maternal

age have become very important (or more accurately, the *ratios* of risk figures at various ages to the risk figure at age 35 (or whatever age boundary is chosen) has become critical). If a risk criterion is missed by a decimal point an amniocentesis may not be performed. In one sense, of course, age is just as arbitrary. A day or a month might decide for or against an amniocentesis. Age can be measured precisely, but not risk for age; there is an uncertainty about any cited risk figure for any particular woman. And precisely what maternal-age risk schedule should be used is still a matter of concern.

There is considerable variation in published risk figures by maternal age for livebirth risk, and the rate schedules in use are based upon extensive data only from those of European (or European ancestral) origin. In the USA, no one makes any adjustment for racial or ethnic variables in risk counseling for Down's syndrome, but the presumption that the published maternal age-specific risk figures derived from the mostly European populations (or rather, the ranges in those figures) apply to the average individual of that age in any ethnic and racial group remains a presumption. There are very few good studies of those of non-European background. Some workers, mostly from an earlier era, have implied lower maternal age-specific rates in some non-European groups (for review of earlier studies see Hook and Porter, 1977). These results are almost certainly attributable to underassessment in non-Europeans. For American Blacks, the best, though small, study found slightly higher rates than in American Whites (Sever *et al.*, 1970; see also Kashgarian and Rendtorff, 1969). There are very few adequate studies in Asians. An interesting study in Malaysia (Boo *et al.*, 1989) compared rates in Malays, Chinese, and Indians but the database was small. Recent data on three racial groups in Birmingham UK (Knox and Lancashire, 1991) appear in Table 1.1. These do not adjust for losses due to prenatal diagnosis but do include stillbirths. They provide some reassurance that rates are likely not to be *higher* in Pakistani or Afro-Caribbeans than in UK whites. Perhaps the UK National Register on Down's syndrome (Mutton *et al.*, 1991) will eventually provide large scale useful data on this issue in the non-European groups in the UK.

Wilson *et al.* (1992) make a plausible case for higher 5-year maternal age-specific rates in Latinos (primarily natives of Mexico and Central America) in Los Angeles than in those of European background. I have recently looked for such trends in all California livebirths by 1-year maternal age interval in data from the California Birth Defects Monitoring Program. The rates appear no higher than the published rates for those

Table 1.1. *Down's syndrome in stillbirths and livebirths in three ethnic groups in Birmingham, UK, 1964–84*

| Maternal age (years) | Caucasians | | Asians | | Afro-Caribbean | |
|---|---|---|---|---|---|---|
| | DS/births | Rate | DS/births | Rate | DS/births | Rate |
| <25 | 91/120 231 | 0.76 | 15/23 538 | 0.64 | 8/11 738 | 0.68[a] |
| 25–29 | 73/79 789 | 0.91 | 19/14 948 | 1.27 | 8/6045 | 1.32 |
| 30–34 | 58/41 456 | 1.40 | 17/7906 | 2.15 | 4/4258 | 0.94 |
| 35–39 | 80/17 323 | 4.62 | 12/4011 | 2.99 | 6/2515 | 2.39 |
| ≥40 | 61[b]/5371 | 11.41[b] | 15/2339 | 6.41 | 8/994 | 8.05 |
| Total | 363[c]/264 170 | 1.37[c] | 78/52 742 | 1.48[d] | 34/25 550 | 1.33[e] |

From Knox and Lancashire (1991) with modification. The rates given here are, with exceptions noted, from Table 3.5 (p. 53) of Knox and Lancashire (1991). The denominator in each age category is from Appendix 2.2, Table iv, (p. 38) and the totals given are the calculated sum in each category. The number of Down's syndrome cases given at each age is calculated, with the exceptions noted, from the age specific rates given in Table 3.5 of this reference and livebirths in each age group.

[a] The entry in the reference (1.74) appears to be a misprint.

[b] The given rate actually 'predicts' 61.3 cases in the number of livebirths given.

[c] Table 3.2 of this reference gives 354 total cases in Caucasians (denominator not specified) and a rate of 1.383 per 1000. The number and rates for other defects in the table imply a denominator about 255 920 total births, smaller than the total of 264 490 cited elsewhere in this reference. The overall difference in rates is trivial, but the two tables imply a difference of at least 363 − 354 = 9 cases in whites total.

[d] 1.47 in the original report (p. 52).

[e] From p. 51 of original report.

of European background, but the available Latino data do not include any prenatal terminations. Prenatal cytogenetic utilization is relatively low in this population for religious and social reasons; underestimates from this loss may not be serious, but there is still a residual uncertainty.

There is evidence for higher rates of Down's syndrome, in the middle part of the maternal age range, in Israeli Jews of Asian or African origin compared with those of European origin (Hook and Harlap, 1979). A problem with both the study in Israel and in Los Angeles is that the data available for reanalysis have been based only upon 5-year intervals (see Table 1.2 for rates in these two groups). Therefore, there is no group which can be confidently stated to have lower maternal age-specific rates than Europeans. Equally, on present evidence, one cannot assume that the average livebirth rates must be the same for all ethnic and racial groups.

Table 1.2. *5-year maternal age-specific rates and ratios of Down's syndrome in two non-European populations per 1000 and ratio to rates in Sweden*

| Maternal age (years) | Sweden | 'Latinos'/LA | Ratio to Swedish rates | Non-European Jews in Israel | Ratio to Swedish rates |
|---|---|---|---|---|---|
| 15–19 | 0.59 | 0.74 | 1.3 | — | — |
| 20–24 | 0.74 | 0.80 | 1.1 | 0.60 | 0.8 |
| 25–29 | 0.88 | 1.02 | 1.2 | 1.23 | 1.4 |
| 30–34 | 1.45 | 2.35 | 1.6 | 2.65 | 1.8 |
| 35–39 | 3.74 | 4.85 | 1.3 | 6.53 | 1.7 |
| 40–44 | 14.96 | 24.22 | 1.6 | 16.54 | 1.1 |

Modified from data in Hook and Harlap (1979) and Wilson *et al.* (1992).

A number of other 'demographic risk' factors have been proposed. The effects of any of these, at least within those of European ancestry, are unlikely to be large. This does *not* exclude the possibility of small effects (certainly of relative risks between 0.5 and 2.0) *nor* the possibility that there are smaller subgroups within intensively studied populations or larger groups in other populations in which these or other factors are associated with large magnitude effects. Inbreeding in Kuwaitis (Alfi *et al.*, 1980) but not in most other groups may be one example and could be explained by recessive genes in *this* particular population which predisposed to non-disjunction. Another possible example is the history of a prior spontaneous (unkaryotyped) abortion, but only in very young women (Hook and Cross, 1983).

An intriguing observation in many studies is the suggestion of a negative association of maternal cigarette smoking (Cuckle *et al.*, 1990; Kline *et al.*, 1993). Though Cuckle tends to dismiss the trend, the summary table appears to provide some supporting evidence consistent with a relative risk of about 0.7 to 0.8. The issue is further complicated by the fact that maternal smoking is associated with higher maternal serum α-fetoprotein (MSAFP) levels (about 3%) and lower human chorionic gonadotropin levels (about 23%) (Palomaki *et al.*, 1993). If cigarette smoking *per se is* established as a (negative) risk factor, then because of the large but variable proportion of smokers in different populations, it will be necessary to re-examine published livebirth rates to estimate how much of the residual variation may be attributable to differences in smoking

habits. This would greatly complicate the application of maternal age-specific rates.

Maternal serum thyroid auto-antibodies are a plausible associated risk (Cuckle *et al.*, 1988) but this is an expensive test relative to its likely contribution. There is also evidence (Khoury *et al.*, 1989) that a maternal history of thyroid disease is a risk factor (relative risk 1.5). This is compatible with the trends with thyroid auto-antibodies and the information would be easy to collect. Similarly, the modest association (1.3- to about 2-fold increase) of maternal bleeding and Down's syndrome that has been reported in several studies (see Cuckle and Wald, 1987 for review) appears plausible. If confirmed and defined more precisely, this could also become an 'adjustment' factor.

One of the most perplexing variables is maternal preconceptual exposure to ionizing radiation. There are some highly suggestive studies in the literature and support from studies in lower organisms. But there are also highly convincing negative results (for review, see Kline and Stein, 1985.) Observations from Hiroshima and Nagasaki argue against an association because there is a (non-significant) *negative* trend (Schull and Neel, 1962). Discrepancies among the radiation studies have spawned a number of hypotheses explaining the differences on the basis of timing or dosage. However, a positive history cannot presently be used to adjust risk. Other factors with at least suggestive associations with Down's syndrome include oral contraceptives and spermicides, but neither has been confirmed (references in Kline and Stein, 1985; Kline *et al.*, 1989).

A separate issue is the 'fine tuning' of estimates of risk derived from existing methods of screening. Each of these issues has been a source of lively controversy, for example:

(1) Do we analyze serum markers using Multiples of the Median (MoMs) or by observed values of MSAFP and other serum proteins adjusted for known sources of variability within a particular laboratory (see Reynold *et al.*, 1993; Wald, 1993)?
(2) Existing methods of risk projection presume not only independence of each of these markers with age and each other over the entire range but also multivariate 'normal', i.e. Gaussian, distributions of the serum markers. Are these assumptions proven? The evidence may (or may not) be *consistent* with such assumptions. A sensitivity test to test the *range* would be worthwhile. (See discussion and references in Hook, 1988, 1989.)
(3) Which *relative* risk schedules for MSAFP and Down's syndrome (i.e.

lists of rates projecting the change in risk associated with a particular MSAFP value) should be used? Three different rate schedules from three different countries, USA, England and Denmark have appeared (Cuckle *et al.*, 1987; Palomaki and Haddow, 1987 and unpublished supplement to this paper; Tabor *et al.*, 1987). The USA group is now using the English schedule (Wald *et al.*, 1989). But it is not clear which is appropriate if there are regional variations. Most workers appear to be using the English reference series, e.g. Zeitune *et al.* (1991), (which has modified the schedule for all trisomies).

(4) How precisely do we derive the estimate for spontaneous losses between amniocentesis and term birth? And should we assume rates under age 20 years continue to decline or level out (Zeitune *et al.*, 1991; Hook, 1985b)?

There is no doubt that biochemical screening enhances risk estimates. But the extent to which some women who would otherwise *receive* amniocentesis are inappropriately deemed as low risk remains a point of concern. The accumulation of data on older women within screening programs will allow evaluation of these projections.

## Some policy issues

Serum screening is improving prenatal detection of affected conceptuses and, with new markers or other prenatal observations, may become even more efficient. One further factor which should be considered is variability in termination.

This pertains to an individual's perception of the risks of amniocentesis and views on pregnancy termination. Among women at risk because of advanced age or other risk factors before the advent of biochemical screening, the proportion in whom Down's syndrome was diagnosed by amniocentesis but who were not effectively terminated was 2–3% in New York State (E.B. Hook, unpublished data). Later studies have reported proportions closer to 10% (e.g. Vincent *et al.*, 1991), but these include cases diagnosed as at risk through maternal serum screening as well as just age. In California, preliminary data suggest that the proportion of non-terminations of Down's syndrome is much higher among women initially detected through serum screening than among those who had amniocentesis only because of age. There may well be social differences between women identified through screening and those who go directly to