Opinion on the detection of the risk of f tal trisomy 21 by blood tests in pregnant women. Report.

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Opinion

The presence of high levels of plasma HCG (Human Chorionic Gonadotropin) around the 16th week of pregnancy justifies the prediction of an increased risk of trisomy 21 in the foetus, thus warranting amniocentesis. However, an abnormal HCG level does not mean that trisomy 21 is certain, and in 20 to 30% of trisomic pregnancies this level may not rise.

For the reasons explained in the report that follows, the CCNE cannot approve a public health programme for the mass systematic detection of trisomy 21, whether by direct means or biological blood tests.

To justify such detection, three conditions should be met :

- those undergoing it should be given prior medical information on the proposed test. This information should be intelligible and adapted to each case, and concomitant psychological assistance should also be proposed ;

- blood tests must be done by an approved laboratory, and

- the tests must be combined with a compulsory consultation with, at least, a biologist-geneticist, and a specialist in foetal echography, in an approved centre for prenatal diagnosis.

Lastly, the CCNE considers that age alone cannot justify covering the cost of such tests, especially those prescribed within the framework of the conditions listed above.

Report

The French Ministry of Health on the one hand, and the National Committee on the Biology of Reproduction on the other, consulted the CCNE about the use, among the population, of biological blood tests to evaluate, in pregnant women, the risk of carrying a child with trisomy 21. Only those women desiring such detection would undergo it.

The serious nature and evolution of trisomy 21 and the absence of any treatment mean that a trisomic pregnancy definitely comes within the scope of the law of 1975 (1) , which provides that the mother can request the termination of her pregnancy by medical means if the prenatal diagnosis is certain. For over 20 years, this diagnosis has been based on the visualization of 3 chromosomes 21 after amniocentesis.

In most cases, diagnosis of trisomy is felt to be " a misfortune for the individual, an emotional ordeal and an economic burden for the family and society" , with no hope of obtaining a perceptible improvement in the life of the trisomic subject.

Present knowledge and techniques still necessitate an analysis of foetal cells after amniocentesis or chorial villosity sampling, to establish a diagnosis of trisomy 21. However, these explorations are invasive and not devoid of risks for the foetus. They lead to between 5 and 15 miscarriages per 1000 persons sampled.

Consequently, the women for whom these tests are suggested must be at a higher risk of giving birth to a trisomic child than the risk involved in such invasive exploration. As a function of the mother's age, the incidence of trisomy 21 at birth is the following :

all ages combined 1/650 births

over 40 years 1/50

38/39 years 1/150

35/38 years 1/300

30/35 years 1/900

20/30 years 1/1500

For subjects aged less than 18 years, epidemiological studies only cover small numbers, their results are contradictory and they do not allow conclusions to be drawn regarding any significant increase with age.

At present, a foetal chromosomal diagnosis is proposed (and reimbursed by Social Security) from the age of 38. However, it should straight away be stressed that such diagnosis does not, in theory or in practice, constitute a programme for the eradication of trisomy. This programme, based on the decision of the fully informed mother, is neither obligatory above the age of 38 nor banned under that age, but for reasons connected with their responsibilities, the health authorities have decided to limit their financial coverage of tests to agegroups above 38 years.

Even if such a programme had been applied to all women over 38, three quarters of trisomic births would have eluded such detection, since many trisomic children are born of younger women, and taken together, it is in the younger agegroup below 38 that the largest number of trisomic births occurs. Barring special circumstances, detection is not applied to these agegroups because the risk is considered small. In addition, the practice of making a cytogenetic diagnosis in women of 38 or more only concerned 14% of these patients in 1981 and 60% in 1991.

Further, present conditions of access to these tests are not satisfactory, and medical practice shows this clearly. The restrictions on payment for these tests by the Health Insurance on the basis of age are not ethical, because there should be equal access to medical explorations. Of course, women not in the over-38 agegroups which are reimbursed by the health authorities can have a cytogenetic diagnosis at their expense if they wish, when their doctor considers the risk of a trisomic birth to be greater than that involved in amniocentesis or chorial villosity sampling.

The measures envisaged today provide for women below the age of 18 and above the age of 30 to have access to a type of detection based on quantitative variations in the biological parameters normally present in the maternal circulation during pregnancy. Henceforth, amniocentesis would be proposed to women exhibiting a significant rise in HCG (2) (estimated in percentiles) as a function of the woman's age and of large variations during the first two trimesters of her pregnancy. In this connection the physiological curve for the decline in HCG makes it necessary to date precisely the time during pregnancy when physiological values are liable to change.

International multicentric studies dealing with over 100 000 women have shown that if such selection for amniocentesis is conducted under indubitably rigorous scientific and technical conditions, this test permits detection of a group comprising 5 to 7% of pregnant women under 38 for whom the risk of trisomy is of the same order as that observed for all pregnant women aged 40 or more, i.e. one in 50, whereas under present arrangements, this invasive test is proposed for a lesser risk.

Moreover, only those requesting such detection would undergo it. The arrangements envisaged do not therefore constitute a mass programme designed to eradicate trisomy. Such a programme would pose formidable problems, as it would mean that any case of trisomy could only be detected by programming amniocentesis for all pregnancies, which would be illusory and unacceptable, because it would require authoritative measures contrary to all ethical considerations. In addition, such a decision would be interpreted as a disavowal by families engaged in bringing up a trisomic child. The CCNE reiterates that in its opinion of May 13, 1985, it stated that " general recourse to such an antenatal diagnosis could only strengthen the social process of rejection of subjects considered abnormal" .

The CCNE therefore believes it should stress the inappropriate ambiguous nature of the term " public health programme" used in the request for its opinion, and the same applies to the proposition that " women over 30 and under 18 could have access to this type of detection" . Such limitations would create an ethico-legal problem with which, moreover, medical practitioners are already familiar.

In relation to the women who are not in the agegroup specified in the ministerial programmes, what is the doctor's responsibility, if he or she either systematically informs patients of the existence of such tests and of their non-reimbursement by the Health Insurance, or if they limit their explanations to those women who clearly express the wish to undergo these tests ? The issue in fact concerns laboratory tests liable to lead to amniocentesis which is not devoid of risks for the foetus, even though the risk of its being trisomic is very small.

Whichever alternative is chosen, practitioners may be liable to reproaches in two cases : injury to the foetus when amniocentesis reveals that it is normal, or the birth of a trisomic child when the test was not performed.

The choice of strategy should be left to the doctor, and be a function of the personality of the woman, who in the last instance has to make the decision. Given the variability of the risk/benefit balance, no generally applicable solution can be proposed. In all cases, it is in doctors' interests to keep a precise record of their reasons for recommending a particular attitude following consultations with the patient, in order to prove, if necessary, that they fulfilled their functions conscientiously.

In the light of these essential comments, the CCNE considers that the objectives thus defined in the programme submitted for its opinion can only be fulfilled and approved on three conditions :

that prior medical information of a high standard is available

that blood tests are only done by approved laboratories, and

that only approved centres are consulted for antenatal diagnoses

The need for prior medical information

Any strategy involving the use of maternal serum markers must, before any sampling, be based on simple, clear and appropriate information, accompanied by psychological assistance for the woman, in order to avoid any confusion in the future mother's mind between the discovery that she belongs to a group at increased risk, and the actual diagnosis of trisomy in the foetus. At the outset, it must be clear to the mother that such detection is only an evaluation of the probability of the risk of trisomy 21, which might subsequently lead to a second examination that would confirm the presence either of a normal karyotype, or of a chromosomal anomaly requiring invasive sampling.

The woman must be assured that she will have complete freedom of decision and that her wishes will be complied with. Similarly, the problem of the couple's attitude to a possible termination of pregnancy must be dealt with before blood sampling. The exertion of any pressure on the mother, however slight, with a view to influencing her decision would be intolerable. Informing her of the results of laboratory tests must remain an essential stage in the medical follow up of such pregnancies.

The extremely conclusive experience of certain maternity hospitals has shown the predominant importance of such information as one of the factors in the decision to measure serum marker levels.

Dehumanized automatically planned application of such a biological programme would cause a couple extreme anxiety. If the couple were not given sufficient information, such application could also lead to a search for responsibility in cases of unpredictable failure of detection. For instance, some of the women whom the health authorities do not consider to be at risk because of their normal HCG levels from weeks 15 to 17 of pregnancy will in fact give birth to a child with trisomy 21. Thus, normal HCG is not in itself a guarantee of normality.

Recourse only to approved laboratories for this type of test

The only laboratories entitled to practise the necessary tests for prenatal diagnosis should be those organized to conduct this policy of detection, whose qualifications and standards of efficiency have been duly checked. The provisions of the Decree of April 8, 1988, on biological examinations in view of a diagnosis relating to an expected child must be rigorously fulfilled, especially as regards specific legal qualifications. Those so qualified should be biologists who are competent in the interpretation of the results, because of the particular characteristics of the biology concerned.

Recourse to co-ordinated centres for antenatal diagnosis

The progress made in the quality of echograms and the competence of echographers raises hopes for more efficient detection in mothers over 30, by signs like early transient thickening of the foetal nucha. This progress constitutes an additional argument in favour of setting up more of such centres.

The CCNE wishes to stress once again the terms of its opinion of May 13, 1985 - which apply particularly well to the present case - regarding the need to organize " approved centres for antenatal diagnosis. The Committee considers it desirable that no decision to terminate a pregnancy should be possible without consulting such a centre, which should be pluridisciplinary and include at least one physician who is a biologist and geneticist, and one specialist in foetal echography" . Such centres should be able to provide women with psychoaffective assistance, whatever their decision.

Notes

1. Under the Law of January 17, 1975, one of the legal motives for the termination of pregnancy is the existence of a strong probability that the child expected will suffer from an especially serious complaint recognized as incurable at the time of diagnosis. Trisomy 21, duly diagnosed, meets the four criteria chosen to define such complaints.

2. Initials standing for Human Chorionic Gonadotropin