



Review

# How unexpected are unexpected findings in prenatal cytogenetic diagnosis? A literature review

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Received 18 March 2004; received in revised form 13 September 2004; accepted 20 October 2004

## Abstract

The objective of this review was to gain understanding about unexpected findings in prenatal cytogenetic diagnosis. This category of results might be excluded from prenatal testing when new molecular tests such as I-FISH and QF-PCR will be applied in a future scenario of targeted testing. The literature was systematically searched for publications wherein the term unexpected or a synonym refers to testing results with specific problems. On the selected articles a qualitative analysis was performed, using the methods of cross-case analysis and within-case analysis. Sixteen articles published between 1979 and 2003 were selected. Analysis led to the classification of four problems of unexpected findings: I. unexpected for professionals; II. unexpected for patients; III. uncertainty; IV. other difficult counselling issues. We conclude that currently the problems of unexpected findings relate only slightly to their unexpected character. Instead, the main problems of unexpected findings relate to uncertainty and other aspects which create difficult counselling issues. As such, unexpected findings can be distinguished only gradually from standard results. Before targeted testing can be applied it is necessary to establish exact criteria in order to discern unexpected findings from standard testing results.

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*Keywords:* Chromosome aberrations; Unexpected findings; Molecular diagnostics; FISH; QF-PCR

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## 1. Introduction

Full karyotype analysis is the gold standard in current prenatal cytogenetic diagnosis [1]. Within this practice, most professionals involved in the process of chromosome analysis of chorionic villi or amniotic fluid are aware of the fact that *any* kind of chromosome abnormality can be detected, not only the one for which the test is actually performed because of an existing high risk (i.e. trisomy 21 in the majority of cases). Still, some testing results in prenatal cytogenetic diagnosis are referred to as unexpected findings [2,3]. Knowing the purpose of full karyotype analysis this seems rather peculiar; why call a specific testing result detected in a practice where *any* testing result might be expected, an unexpected finding?

Although our research group has had a consistent interest in the topic of unexpected findings [4–6], some confusion about the exact meaning of this specific term was also signalled within our own centre. When we recently started a new research project about how to communicate about unexpected findings—a project of which the results will be published later—we first tried to agree on the exact meaning of the term unexpected findings. Although most professionals were familiar with the literature about this topic, this proved to be difficult. When asked about what an unexpected finding would be from their own practical perspective, most lab technicians and cytogeneticists replied: ‘How do you mean, unexpected? The more peculiar the aberrations we find, the more excited we get, so why call an unusual marker chromosome or other rare structural aberrations an unexpected finding anyway?’

Clinical geneticists took a different stance because they tended to identify more with the patient’s perspective. Still, they too, have their doubts about the exact meaning of the term. Although they do differentiate between testing results because much more professional skills are needed to communicate for instance a mosaicism than to communicate a trisomy 21, they know on the other hand that for the patient *any* detected chromosome aberration is unexpected, even a ‘standard’ trisomy 21. So we acknowledged that—at least in our own centre—the meaning of the term unexpected findings is not so obvious.

Still, the word unexpected is regularly used in the prenatal diagnosis literature, even recently, for instance in publications about new possible applications of molecular tests like interphase fluorescent in situ hybridization (I-FISH) and quantitative fluorescent polymerase chain reaction (QF-PCR). The initial reason to apply such molecular tests in prenatal diagnosis was to process testing results more rapidly [7–9]. QF-PCR has already been implemented within a routine service [1]. Currently, such rapid testing of amniotic fluid or chorionic villi is always followed by the gold standard of full karyotype analysis, but the possibilities to apply these molecular tests as a stand alone technique are also being examined now [10].

Consequences perceived before as a disadvantage, i.e. that the molecular tests do not address the possible presence of unexpected chromosome abnormalities [2], are now sometimes presented as a possible benefit [11]. One of the promises is that application of such targeted testing would relieve parents of the burden of unexpected and incomprehensible results [11].

But which unexpected findings are exactly referred to in this context? Based on our own experiences with the concept of unexpected findings this is not clear. Therefore, we reviewed the literature to examine how the term unexpected findings has been used through the years. To be able to fully understand the possible benefits of targeted testing, presented as a solution for the problems of unexpected findings, we believe it is imperative to gain more insight into the topic of unexpected findings first.

## 2. Methods

### 2.1. Literature search

Literature was searched for articles in which problems of specific testing results of chromosome analysis were described under the heading ‘unexpected findings’.

First of all, four different PubMed searches were performed for the term unexpected(ly) and three of its synonyms. Searches were performed for prenatal diagnosis (MeSH term) AND Unexpected(ly); Prenatal diagnosis AND Incidental(ly); Prenatal diagnosis AND Coincidental(ly); Prenatal diagnosis AND Unusual, limited for the English language only. These 4 searches respectively retrieved 119, 72, 25, and 392 publications, which were selected by reading titles and abstracts. Included were all publications which described problems of a specific category of testing results of chromosome analysis after amniocentesis or chorionic villi sampling under the heading ‘unexpected findings’ or a similar term. Excluded were publications which reported about results of other prenatal tests, e.g. ultrasound or DNA diagnostics; single case reports; follow up reports and/or specific indications.

Secondly we searched in our own archives of publications about sex chromosome abnormalities, which consisted of about 50 articles from the period 1978–2003, by using the same inclusion and exclusion criteria as in the PubMed search.

Thirdly, we searched in our own archives of reported series of amniocentesis ( $n = 29$ ; period 1966–1988) and chorionic villi sampling ( $n = 27$ ; period 1984–1995), by using the same inclusion and exclusion criteria.

### 2.2. Analysis

The selected articles were analysed both in a quantitative and qualitative way to examine how the term unexpected

findings has been used in the literature. The concrete questions used in the analysis were:

- Which exact terms are used? How often? In which section of the article are the terms mentioned?
- Which problems are described under the heading ‘unexpected findings’ or its synonym?

Two types of qualitative analysis were used, i.e. a within-case analysis and a cross-case analysis [12]. In the within-case method all publications were analysed one by one. The usage of the term ‘unexpected findings’ was examined in relation to the main message of the article and in relation to the different sections of the article, e.g. introduction, results and conclusion/discussion. Through the cross-case analysis the usage of the term ‘unexpected findings’ was compared between publications.

### 3. Results

Through the PubMed search for Prenatal Diagnosis AND Unexpected(ly) we selected ten publications in which problems of specific testing results of chromosome analysis were described under the heading ‘unexpected findings’ or a synonym [2–5,13–18]. No additional publications were selected from the other three PubMed searches. Another five articles were selected from our own archive of publications about sex chromosome anomalies [19–23]. One last article was found in our own archive of reported series of amniocentesis and chorionic villi sampling [6]. Our analysis presented in this paper is based on these 16 publications. Table 1 presents the most relevant details of the sixteen selected publications mentioning the word ‘unexpected’ or one of its synonyms.

In 3 of the 16 publications the term unexpected(ly) was not mentioned, but a synonym was used instead, i.e. fortuitous(ly) or chance finding. Some of the articles which did mention the word unexpected also mentioned one or more synonyms, like incidental, coincidental or unanticipated. The sixteen articles we selected were published between 1979 and 2003, with a majority dated in the 1980s, and were published in specialised as well as in general medical journals. In 10 of the 16 publications the word unexpected or its synonym was mentioned in the title and/or the abstract, which indicates that the unexpected findings were an important topic of the publication. Other sections of the article in which the term unexpected or its synonym was mentioned were the introduction ( $n = 5$ ), results ( $n = 5$ ), discussion ( $n = 6$ ) and/or elsewhere in the article ( $n = 5$ ). Six of the 16 articles mentioned the word unexpected or its synonym only once; in the other 10 publications the term was used twice or more.

In five publications the word unexpected specifically referred to some kind of structural chromosome rearrangement [5,14–17]. In six publications (some kind of) sex chromosome abnormality was specifically discussed [18–23]. In the other five publications the term unexpected was used to label a mix of different kind of chromosome abnormalities, varying from trisomy 21 [13] and trisomy X [6] to marker chromosomes [4] and a collection of all kind of unexpected chromosome abnormalities in the two articles which give a more systematic overview of unexpected findings [2,3].

Our analysis of the literature led to the classification of four kinds of problems mentioned under the heading unexpected findings, which are described in the following section.

Table 1  
Publications ( $n = 16$ ) mentioning ‘unexpected’ or its synonym

Reference	Year of publication	Mentioned phrase	Testing result(s) referred to
[13]	1979	Unexpected finding; Unexpected translocation; Coincidental finding	Translocations; Triploid; trisomy 18; trisomy 21 while tested for other indications
[15]	1980	Unexpected translocation	Translocations
[6]	1981	Unexpected findings	De novo apparently balanced aberrations; Mosaicism; Trisomy X
[14]	1982	Unexpected chromosome rearrangement	Structural chromosome rearrangements
[19]	1982	(Detected) incidentally and unexpectedly	SCAs
[16]	1984	Unexpected/Unsuspected/Unanticipated structural chromosome rearrangement; (detected) incidentally	Inherited structural chromosome rearrangements
[17]	1984	Unexpected structural chromosome rearrangements	Structural chromosome rearrangements
[20]	1986	Fortuitous diagnoses	Turner syndrome
[21]	1987	Unexpected and incidental (detection)	SCAs
[4]	1987	Unexpected abnormalities	Equivocal laboratory findings in chorionic villi sampling (CVS)
[5]	1989	Unexpected balanced chromosome rearrangements	Balanced chromosome rearrangements
[2]	1993	Unexpected (laboratory) findings; Unexpected chromosome abnormality	De novo apparently balanced structural rearrangements; De novo marker chromosomes; mosaicism; SCAs
[3]	1999	Unexpected cytogenetic findings; Unexpected result; Unexpected aneuploidy	Trisomy 13 and 18; Structural abnormalities; mosaicism; SCAs
[18]	2001	Unexpected result	SCAs
[22]	2002	(Discovered) fortuitously	Klinefelter syndrome
[23]	2003	Chance finding	SCAs

## 4. Problems of unexpected findings

### 4.1. Unexpected for professionals

Several early publications report about testing results which were detected unexpectedly for professionals who were not yet acquainted with the new technique of analysing chromosomes derived from amniotic fluid or chorionic villi.

The earliest publication [13] presents several testing results which did not match with the indication that had been the reason for testing. The abnormal results reported in this article were trisomy 18, triploidy and trisomy 21 when the indication was an increased risk for another aberration than the one detected.

Four other publications [14–17] elaborate on the detection of a structural chromosome rearrangement which “occurs more frequently than expected from the results of studies of liveborn children” [14]. To make professionals aware of the high frequency of structural anomalies found when testing is done for common indications like advanced maternal age, exact incidences were reported in these publications.

In 1982 it is discussed what should be done when a sex chromosome abnormality (SCA) is found, especially what to tell the parents in such a case. At that time it was not even obvious *that* professionals would inform their patients about this result. Once an SCA was detected, professionals faced the dilemma of choosing between not telling, which might be defensive in law, and discussing the finding of an SCA in full length with the parents. The latter option was problematic in the early times of prenatal diagnosis due to “the almost total lack of accurate and unselected information on the likely prognosis for affected individuals, resulting in confusion as to what parents are told and an understandable reluctance to transmit information which might prove to be erroneous” [19]. In the last 20 years the knowledge about SCAs has enormously improved because several prospective studies have been conducted in which children with SCA from unselected populations were followed from birth [18].

One publication reports the unexpected detection of some chromosome aberrations—of which the phenotypical consequences could not be predicted—which are not in accordance with the aim of prenatal diagnosis, a phenomenon that seems to have caught the authors by surprise: “As the aim of prenatal chromosome analysis is the diagnosis of severe congenital anomalies, we were struck by this high percentage of troublesome findings” [6]. A similar problem is reported in an article which describes testing results like mosaicism and marker chromosomes found in the chorionic villi procedure but not in the subsequent amniocentesis [4]. The aim of these publications at the time was to make professionals aware of that so far unknown phenomenon.

### 4.2. Unexpected for patients

Along with the awareness of professionals with regard to the phenomenon of detecting testing results which *they* had

not foreseen, the awareness grew that these testing results would be unexpected for patients as well.

The problem that patients might not anticipate the detection of certain testing results is discussed most extensively in the literature about the SCAs. In 1982 it is already signalled that it is “not common practice to discuss sex chromosome abnormalities, as a potential problem, before the test” [21]. A more recent publication illustrates this is currently still the case: “While some parents are given information about the condition before testing, it seems that most are not” [22]. To prepare parents for the unanticipated detection of an SCA it is already suggested in 1987 to mention this in the pre test counseling: “It might be better to incorporate such a topic into a pre-pregnancy counselling program, or into an educational programme linked with school leaving” [21].

Not only for the SCAs it is suggested to make patients aware of through pre test counselling, but also with regard to other testing results which might be unforeseen for professionals as well as for patients: “In our team it is the practice to point out the possibilities of such unexpected findings when counselling the couple preceding amniocentesis” [6]. For pre-test counselling preceding a chorionic villi sampling the more specific advice is: “Counselling before chorionic villi sampling should include the possibility that subsequent amniocentesis may be needed should mosaicism or some other unexpected abnormality be detected” [4]. More general advice is given in publication 13: “It seems prudent to point out during prenatal genetic counselling that while advanced maternal age with concerns for Down syndrome is usually known by the counselee, there exists an equal risk of some other aneuploidy which might carry a more or less severe prognosis than Down syndrome” [3].

### 4.3. Uncertainty

In general terms, the problem of uncertainty of some testing results is already described rather boldly in 1979 as: “Prenatal diagnosis, in contrast to diagnostic cytogenetics, is “black box” cytogenetics, in that it is done without a known phenotype with which to correlate the results” [13].

More specifically, this problematic aspect of the structural chromosome rearrangement was described by Boué et al. by summing up the following three questions, raised when a structural anomaly is found in fetal cells: “Is this anomaly balanced or unbalanced? Is it inherited or de novo? If de novo and apparently balanced, is the fetus expected to be normal?” [14]. With regard to the last question it was already concluded in the 1980s that “Each de novo reciprocal translocation is different from the others and no definite risk figures can be calculated” [14]. This means that “It can never be decided with 100% certainty whether the child will be healthy or not” [17]. In sum, for some testing results the situation is as follows: “For a de novo apparently balanced reciprocal translocation one can only cite an 8–10% risk of mental retardation which is not likely to be altered by further cytogenetic or ultrasonographic study” [3].

The specific problems of uncertainty regarding mosaicism are summarized as follows: “The detection of mosaicism or suspected mosaicism in prenatal diagnostic specimens raises issues of two types. The first is related to the laboratory interpretation of the findings, that is, does the finding in culture represent the true status of the amniotic fluid or chorionic villi? The second is related to the clinical importance of the findings: How likely is it that the mosaicism detected in culture is representative of the true status of the fetus? and What is the prognosis for the fetus after the finding of true mosaicism for the abnormality in question?” [2].

One conclusion in the literature is that this situation of uncertainty with regard to structural anomalies and mosaicism demands an “experienced and conscientious staff” [13]. It is also concluded that when there is uncertainty about the exact meaning of the results, genetic counseling is complicated. The 1999 article’s suggested strategy in this matter is: “To gather the best information available and to present it to the woman in a non-directive way. The aim is to allow her to make a fully informed decision which the counselor then supports” [2]. However, this is a difficult situation for both professionals and patient, as is illustrated in the following comment: “Once an unexpected result is obtained, prompt genetic counseling [has to be given] by an experienced counselor who is prepared to provide the time and information necessary for couples to grapple with new information, considerable anxiety and a real measure of uncertainty” [3].

#### 4.4. *Other difficult counselling issues*

Beside the uncertainty of some testing results there are other reasons why some testing results lead to difficult counselling issues. These issues have been described specifically for the SCAs, but it is not easy to reveal the exact origin of these counselling difficulties. Apart from the fact that it is an unanticipated situation for the parents to learn about the diagnosis SCA, several other aspects are mentioned in the literature: “Sex chromosome abnormality is far less damaging to the phenotype” [21]. “For most SCAs, the prognosis is milder and less predictable than trisomy 21, and therefore parents are faced with a difficult decision regarding the option of pregnancy termination” [18]. “In this unfamiliar and ambiguous situation they have to make a quick decision whether to continue or terminate the pregnancy” [18]. So apart from the fact that an SCA is an unexpected result for parents, it is also pointed out that some typical aspects of the SCAs make it more difficult for the parents to decide about the continuation of the pregnancy.

As with the uncertain testing results (see category III) some kind of (intensive) post-test counselling is suggested to support parents in their difficult decision making once they have received the diagnosis SCA [2,3]. In addition to the literature about the uncertain testing results, the complex relationship between the professionals’ process of genetic

counselling on one hand and the parents’ process of decision making on the other hand is specifically elaborated on: “Since most parents are unprepared for the diagnosis of an SCA and very few are familiar with these conditions, the information given by health professionals is likely to be of critical importance in guiding their decisions about the pregnancy” [23]. The more recent publications in our study have therefore examined some factors in post diagnostic counselling which might influence these decisions, like health professional’s specialty [22] and the amount of positive or negative information about the SCA communicated by the health professional [23]. The overall conclusion is that the counselling following the diagnosis SCA should meet certain standards: “Lengthy and repeated genetic counselling may be required to ensure that the couple is prepared to make an informed decision about the pregnancy” [3]. And: “Our results suggest an urgent need in training health professionals providing prenatal diagnostic services to ensure first, that they are well informed about the conditions that can be diagnosed as part of their services, and second, that they have the skills to present such information in ways that facilitate parents making an informed choice” [23].

## 5. Comment

The four kinds of problems discussed in the literature under the heading unexpected findings show a great variety and refer to different testing results. The problem of unexpectedness for professionals (category I) has been mentioned specifically for the structural chromosome rearrangements and the SCAs. However, this problem does not exist anymore, since professionals are now fully acquainted with the technique of full karyotype analysis in prenatal cytogenetic testing. The problem of unexpectedness for patients (category II) has been described specifically for the SCAs. The suggested solution for this problem is to mention the SCAs—and other unexpected findings—in the pre test counselling. The two other problems, i.e. uncertainty (category III) and other difficult counselling issues (category IV) are problematic for both professionals and patients and less easy to solve. The problem of uncertainty has been discussed particularly for structural chromosome rearrangements and mosaicism. To handle this uncertainty it is suggested to gather the best information available and to present it in a non-directive way. Other difficult counselling issues have been described particularly for the sex chromosome anomalies. The suggested strategy in this matter is to counsel the patient in such a way that informed choice is facilitated.

Knowing the main problems of the unexpected findings, i.e. uncertainty and other difficult counselling issues, it is still hard to tell how unexpected findings could be distinguished from testing results which are apparently perceived as more standard. After all, how reasonable is it to

assume that the problems of uncertainty and other difficult counselling issues play a role *only* in case of the unexpected findings? Is a standard aberration like trisomy 21 always indisputable? Down's syndrome can vary from a relatively mild to a more severe clinical picture, so even the prognosis of a trisomy 21 is ambiguous or unpredictable to some extent. And counselling in the more standard cases do not necessarily have to be easy. It would therefore be more realistic to conclude that the problems of uncertainty and difficult counselling issues are only *more* apparent in case of the unexpected findings. Instead of the existence of some sharply outlined category suggested by the common use of the term unexpected, we should perceive the difference between unexpected findings and standard results as a *gradual* distinction.

The common use of the term unexpected findings has not had a major influence on the practice of prenatal diagnosis so far. However, the application of targeted testing as described in the introduction would mean a radical change in this matter. Instead of intensifying professional procedures on an individual and ad hoc basis, as is the current strategy in case of an unexpected finding, targeted testing suggests a more structural solution to deal with this problem. In a future scenario of targeted testing the unexpected findings would simply be excluded from the practice of prenatal diagnosis, which would then only be targeted on a selective set of chromosomes, for instance the chromosomes 13, 18 and 21.

When assessing this idea of targeted testing, the following conclusions of our literature review should be taken into account. Firstly, as said above, the literature about unexpected findings does not give a definite clue about the exact distinction between the unexpected findings and standard testing results. However, targeted testing can only be applied when a clear distinction can be made between the target, i.e. the results to be included into the practice of prenatal diagnosis, and the unexpected findings, i.e. the results to be excluded from prenatal diagnosis. Since clear criteria for this distinction can not be found in the literature, these criteria have to be established first.

Secondly, the two main problems of unexpected findings, i.e. uncertainty and other difficult counselling issues, are quite dissimilar. Therefore, an important question is: To which problems exactly would targeted testing be the solution? And how would this solution of targeted testing relate to other possible solutions, like the improvement of pre and post test counselling? The answer to these questions depends on the medical context in which prenatal diagnosis is performed, and different professionals may have a different focus in this matter. For instance, the obstetricians' attitude may have changed because of the increasing use of nuchal translucency measurement (NTM). The detection of Down's syndrome is a much more specific goal of NTM than it is for general cytogenetic diagnosis. So obstetricians may already be focused more exclusively on finding Down's syndrome than most cytogeneticists are in the current practice of prenatal diagnosis. So, as mentioned in the earlier

publications, the category of unexpected findings remains related to the specific indication for which prenatal diagnosis is performed. Yet another complication is that application of targeted testing might lead to a *new* category of unexpected findings, associated with either new or familiar problems.

Thirdly, the literature about the problems of uncertainty and the difficult counselling issues does not always differentiate clearly between the professional's and the patient's perspective. Still, the consequences of these problems vary of course between professionals and patients. Therefore, both these perspectives need to be represented in the discussion about targeted testing in relation to unexpected findings. This is imperative because it still remains to be determined *who* may have to decide about the specific content of the target: the professionals, patients or other parties such as policy makers or financial institutes.

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