OBSTETRICS

Karyotype versus genomic hybridization for the prenatal diagnosis of chromosomal abnormalities: a metaanalysis

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OBJECTIVE: The aim of this study was to determine the diagnostic accuracy of comparative genomic hybridization (CGH) compared with karyotyping for the detection of numerical and structural chromosomal alterations in prenatal diagnosis.

STUDY DESIGN: A metaanalysis was performed using searches of PubMed, EMBASE, CENTRAL, Cochrane Register of Diagnostic Test Accuracy Studies, Google Scholar, gray literature, and reference manuals. No language restriction was imposed. We included cross-sectional, cohort, and case-control studies published from January 1980 through March 2014 in the analysis. Studies of pregnant women who received chorionic villus biopsies, amniocentesis, or cordocentesis and then underwent CGH and karyotype analysis were included. Two independent reviewers assessed each study by title, abstract, and full text before its inclusion in the analysis. Methodological quality was assessed using QUADAS2, and a third reviewer resolved any disagreement. Conclusions were obtained through tests (sensitivity, specificity, and likelihood ratios) for the presence of numerical and structural chromosomal abnormalities. The reference used for these calculations was the presence of any abnormalities in either of the 2 tests (karyotype or CGH), although it should be noted that in most cases, the karyotyping test had a lower yield compared with CGH. Statistical analysis was performed in RevMan 5.2 and the OpenMeta[Analyst] program.

RESULTS: In all, 137 articles were found, and 6 were selected for inclusion in the systematic review. Five were included in the metaanalysis. According to the QUADAS2 analysis of methodology quality, there is an unclear risk for selection bias and reference and standard tests. In the other elements (flow, time, and applicability conditions), a low risk of bias was found. CGH findings were as follows: sensitivity 0.939 (95% confidence interval [CI], 0.838–0.979), $I^2 = 82\%$; specificity 0.999 (95% CI, 0.998–1.000), $I^2 = 0\%$; negative likelihood ratio 0.050 (95% CI, 0.015–0.173), $I^2 = 0\%$; and positive likelihood ratio 1346.123 (95% CI, 389–4649), $I^2 = 0\%$. Karyotype findings were as follows: sensitivity 0.626 (95% CI, 0.408–0.802), $I^2 = 93\%$; specificity 0.999 (95% CI, 0.998–1.000), $I^2 = 0\%$; negative likelihood ratio 0.351 (95% CI, 0.101–1.220), $I^2 = 0\%$; and positive likelihood ratio 841 (95% CI, 226–3128), $I^2 = 10\%$.

CONCLUSION: This systematic review provides evidence of the relative advantage of using CGH in the prenatal diagnosis of chromosomal and structural abnormalities over karyotyping, demonstrating significantly higher sensitivity with similar specificity.

Key words: chromosomal abnormalities, comparative genomic hybridization, karyotype, prenatal diagnosis

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Prenatal studies include the detection of numerical and structural chromosomal abnormalities. However, sampling of fetal genetic material requires the use of invasive procedures that pose risks for both the mother and child.[1] For this reason, a series of screening tests is performed prior to fetal chromosomal analysis to determine if there is a probability ≥1% of finding a chromosomal abnormality. Parameters such as maternal age, biochemical test results, and ultrasound markers, such as fetal anatomy defects, justify performing the more invasive procedure.[2]

The most common diagnostic test for chromosomal abnormalities is G-banding karyotyping. Other tests include fluorescent in situ hybridization (FISH) or quantitative fluorescent polymerase chain reaction. Karyotyping can detect numerical chromosomal abnormalities in chromosomes as well as structural changes, such as the loss or gain of upwards of 5 megabases of genetic material. Other techniques detect common trisomies and monosomies (13, 18, 21, X,

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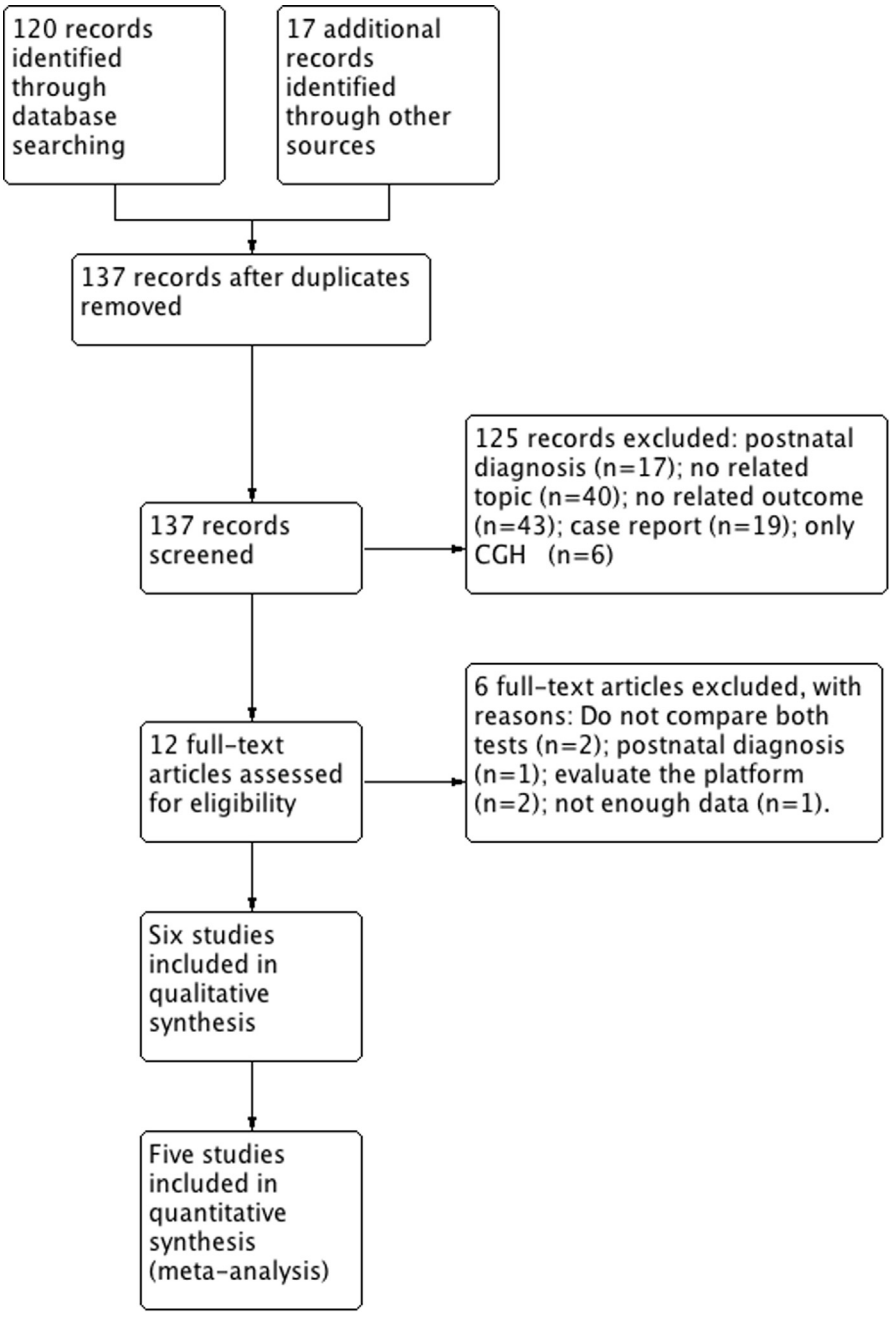
FIGURE 1
Flowchart



CGH, comparative genomic hybridization.

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and Y), in addition to fetal chromosomal sex, but do not diagnose structural alterations.[3] The aforementioned tests are techniques often combined with karyotyping because results are available in approximately a week, whereas karyotyping requires 2-3 weeks.

Comparative genomic hybridization (CGH) has emerged as a molecular test for chromosomal analysis and it is used in prenatal diagnosis, pediatric patients, or adults with specific indications. CGH detects microdeletions and microduplications sizing upwards of 500 pairbases that are not detected by karyotype. In 2010, a consensus document[4] and an economic analysis[5] were published that suggested that CGH should be considered the first diagnostic test, replacing karyotyping in patients with neurological problems, autism, and cognitive deficits and in newborns with congenital anomalies of unknown etiology.

In prenatal diagnosis, studies comparing different chromosomal alteration analysis techniques in high-risk patients report diagnostic frequencies between 2.5-4.2% with karyotyping,[6] whereas frequencies of 5.3-15% have been reported with CGH.[7-10] The detection increases significantly for CGH (9.3-39%) when fetal anatomic defects are indicated.[8,9,11] The patient is not subjected to additional risk, and results are obtained more rapidly. However, there is an increase in the cost as well as the probability of finding variants of an uncertain nature.[7,10]

Given the advantages of CGH over karyotyping in prenatal diagnosis, the use of this molecular test has increased in countries where the additional cost is borne by health insurance as well as in countries or states where abortion is permitted. So far, there was only 1 metaanalysis[12] suggesting that CGH increases the detection rate to diagnose chromosomal abnormalities for prenatal indications overall. That metaanalysis focused on the agreement between both tools and the detection rate of chromosomal abnormalities, however it was not related to diagnostic accuracy.

The aim of this study was to determine the diagnostic accuracy of CGH and karyotyping compared with the sum of the results of the 2 tests for the detection of numerical and structural chromosomal abnormalities in prenatal diagnosis.

Materials and Methods

This study was conducted according to the recommendations of the Cochrane Collaboration and is reported following the PRISMA Statement. The protocol was registered in the international prospective register of systematic reviews (PROSPERO): CRD42014007627.

We designed a search strategy for studies published in MEDLINE via

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