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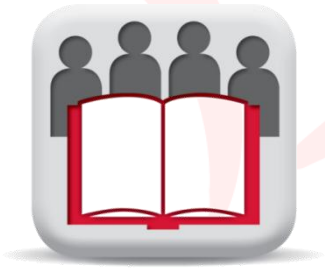
UOG Journal Club: March 2015
UOG 杂志俱乐部：2015年3月

Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis

最新的Meta-分析：通过对母体外周血中游离DNA的分析来筛查胎儿非整倍体

MM Gil, MS Quezada, R Revello, R Akolekar and KH Nicolaides

Volume 45, Issue 3, Date: March (pages 249–266)



Journal Club slides prepared by Dr Shireen Meher
(UOG Editor for Trainees)

Cell-free DNA in screening for aneuploidies
MM Gil et al., UOG 2015

Introduction引言

- Cell-free (cf) DNA in maternal blood may be used to screen for trisomies 21, 18 and 13 and sex chromosome aneuploidies.
- 母体外周血中游离DNA可用来筛查13,18,21三体和性染色体非整倍体

- Numerous studies have reported the clinical validation and/or implementation of using this test strategy.
- 大量的研究已经报道了临床验证和/或实行这个试验策略

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Aim of the study
研究目的

To review clinical validation or implementation studies of maternal blood cell-free (cf) DNA analysis in screening for aneuploidies, and define the performance of screening for fetal trisomies 21, 18 and 13 and sex chromosome aneuploidies.

回顾性分析母体外周血中游离DNA筛查非整倍体的临床验证或实施的研究，并定义其对13,18,21三体及性染色体非整倍体筛查的绩效

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Methods
研究方法

Study design: systematic review 研究设计：系统回顾

Search strategy:检索策略：

- Pubmed, EMBASE and The Cochrane Library were searched for articles published between January 2011 (first such study published) to 4th January 2015.
- 搜索从2011年1月到2015年1月4号在Pubmed， EMBASE 和 The Cochrane Library已发表的文章
- Search terms used: 'maternal blood cfDNA', 'non-invasive prenatal detection', 'noninvasive prenatal diagnosis' or 'non invasive prenatal diagnosis'.
- 搜索条件：“母体外周血游离DNA”，“无创性产前检查”，“无创性产前诊断”
- Reference lists of reviews and relevant original articles were searched
- 搜索综述和相关原著文献作为参考文献
- Searches were restricted to English language publications
- 搜索仅限于英文期刊

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Methods研究方法

- Inclusion criteria 纳入标准
  - Peer-reviewed studies reporting on clinical validation or implementation of prenatal detection maternal cfDNA testing in screening for aneuploidies
  - 同行评审的研究报道，关于临床验证或实施研究母体外周血中游离DNA测试对非整倍体的筛查
  - Data on pregnancy outcome were provided for more than 85% of the study population
  - 提供妊娠结局的数据占研究对象的85%以上

  Exclusion criteria排除标准
  - Studies in which the laboratory carrying out the tests knew fetal karyotype or pregnancy outcome

  由实验室进行测试已知道胎儿核型或妊娠结局的研究
- Two review authors assessed abstract citations for potentially eligible studies
- 两个评审作者评估文摘的引文作为可能合格的研究
- Methodological quality of selected studies was assessed using the QUADAS-2 tool
- 使用UADAS-2工具对已选择研究的质量方法学进行评估
- Meta-analysis was carried out and results presented as summary statistics with 95% Confidence Intervals (CI), using both fixed- and random-effects models, using the statistical package StatsDirect
- 进行Meta分析，结果使用95%可信区间(CI)汇总统计，使用固定和随机模型, 利用StatsDirect统计软件包
- Heterogeneity was assessed using I^2 and Cochran's Q
- 异质性使用I^2和Cochran's Q评估

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Results
研究结果

• Of the 1399 potentially eligible citations retrieved, 37 relevant studies were included in the meta-analysis
•找到1399个可能合格的引文检索,37个相关研究包括在Meta分析中

• Studies were retrospective (*n* = 8), prospective (*n* = 22) or both (*n* = 2)
•回顾性研究(n = 8)、前瞻性研究(n = 22)、两者都有的研究(n = 2)

• Five studies reported on the general population and all others involved high-risk groups
•5个研究报道了普通人群，其他都是高危人群

• One of three methods was used for cfDNA analyses in the included studies
•列入的研究中用三种方法中的一种做cfDNA分析

• There was a wide range in gestational age at time of testing
•测试期间，孕龄的波动范围很大

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Results: methodological quality using QUADAS-2

结果:使用QUADAS-2质量方法学

- Patient selection **病人选择**
  - All except 4 studies were at high risk of bias because 除了4项研究所有的都是偏倚高风险，因为
    - Samples were not stated to have been consecutive or selected randomly, or studies used a case–control design 采样没有阐明连续或随机选择,或使用病例—对照设计
- Index test **指数测试**
  - Low risk of bias in most papers as studies stated the laboratory did not have prior knowledge of test results or pregnancy outcome
  - 在大多数文章是偏倚低风险的，因为实验室研究中没有测试结果或妊娠结局的先验知识
- Reference standard **参考标准**
  - Although most studies at low risk of bias, 4 sex chromosome aneuploidy studies at higher risk of bias because assumption of normal karyotype was made on clinical examination at birth, not on karyotyping
  - 尽管大多数研究是偏倚低风险,4项性染色体非整倍性研究的偏倚是相对高风险的，因为出生后临床检查正常就假设为正常核型,而不是核型检查
- Time and flow **时间和流程**
  - All except 6 studies at high risk of bias because除了6项研究以外偏倚都是高风险,因为
    - Testing not carried out or did not provide results in all cases
    - 不是所有病例都进行测试或提供结果
    - Follow-up not complete
    - 随访不彻底
    - Method for determining outcome was not same in all cases, i.e. clinical examination/karyotyping
    - 测定结果的方法并不是在所病例有中都相同,如临床检查/核型

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Results结果

Aneuploidy 非整倍体	**No. of studies** 研究数	**No. of affected fetuses** 受影响的胎儿数	**No. of unaffected fetuses** 未受影响的胎儿数	**Pooled detection rate (95% CI)** 合并检出率（**95%CI**）	**Pooled false-positive rate (95% CI)** 合并假阳性率（**95%CI**）
Trisomy 21 21三体	24	1051	21 608	99.2% (98.5 to 99.6%)	0.09% (0.05 to 0.14%)
Trisomy 18 18三体	21	389	21 306	96.3% (94.3 to 97.9%)	0.13% (0.07 to 0.20%)
Trisomy 13 13三体	18	139	18 059	91.0% (85.0 to 95.6%)	0.13% (0.05 to 0.26%)
Monosomy X X单体	16	177	9079	90.3% (85.7 to 94.2%)	0.23% (0.14 to 0.34%)
Other sex aneuploidies 其他性染色体非整倍体	12	56	6699	93.0% (85.8 to 97.8%)	0.14% (0.06 to 0.24%)
Trisomy 21 in twins 双胎中的21三体	5	31	399	93.7% (83.6 to 99.2%)	0.23% (0.00 to 0.92%)

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Results结果

- Result from general population studies for trisomy 21
- 从普通人群的研究结果得出21三体
  - 5 studies; 57 affected fetuses, 8685 unaffected fetuses
  - 5研究; 57个受影响胎儿,8685个未受影响胎儿
  - Detection rate 100% with FPR of 0.08%
  - 检测率100%,假阳性率0.08%

- No-result rate of cfDNA test reported as 0% to 12.2%
- cfDNA测试报告无结果率为0%到12.2%
  - Blood collection and transport failure: 0.03% to 11.1%
  - 血液采集和转运失败:0.03%到11.1%
  - Low fetal fraction: 0.5 to 6.1%
  - 低胎儿片段含量:0.5到6.1%
  - Higher for sex chromosome aneuploidies than trisomies (17% *vs* 6.9 %; $P < 0.0001$)
  - 性染色体非整倍性比三体高 (17% vs 6.9%;P < 0.0001)

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Discussion讨论

- cfDNA screening has a detection rate of over 99% for trisomy 21 with a false-positive rate (FPR) of less than 0.1%.
- cfDNA筛查21三体的检出率超过99%，假阳性率(FRP) 不到0.1%。
- Detection rates for trisomy 18 and trisomy 13 are lower, 96% and 91% respectively, with a combined FPR of 0.26%.
- 18三体和13三体检出率低一些,分别为96%和91%，组合假阳性率为0.26%。
- Detection rates for monosomy X and other sex chromosome aneuploidies are 90% and 93% respectively, with FRP of 0.37%, but test failure rate is higher.
- X单体和其他性染色体非整倍体的检出率分别为90%和93%,假阳性率为0.37%,但测试失败率较高。
- Expanding cfDNA testing to include trisomies 18 and 13 would increase the FPR from 0.09% to 0.35% and including sex aneuploidies would increase the FPR further to 0.72%.
- •扩大cfDNA测试包括18三体和13三体会使假阳性率从0.09%提高到0.35%,包括性染色体非整倍体假阳性率将进一步提高到0.72%。
- Performance of cfDNA screening may be worse in twins as compared to singleton pregnancies, with a higher test failure rate.
- 与单胎妊娠相比，在双胎妊娠中，cfDNA筛查的效能会差一些，测试失败率较高。

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Discussion讨论

- Detection rate and FPR in studies in the routine population were similar to high-risk groups
- 在普通人群中检出率和假阳性率类似于高危人群
- Ability to detect aneuploidy with cfDNA analysis is likely to be more dependent on assay precision and fetal DNA percentage, rather than disease prevalence
- cfDNA分析检测非整倍体的能力可能会更加依赖分析精度和胎儿DNA的百分比,而不是疾病患病率
- Test failure may be higher in aneuploid fetuses with trisomy 18 and 13, hence true detection rates may be lower
- 测试失败在18和13三体胎儿中可能更高,因此真正的检出率可能较低
- Risk of bias in sex chromosome aneuploidies is likely to be higher where assessment of outcome was only performed by clinical examination rather than karyotyping
- 与核型检查相比，仅仅由临床检查得出的结果评估时，性染色体非整倍体的偏倚风险可能会更高
- Heterogeneity among studies was low for all analyses, but higher for trisomy 13, where I^2 was 21.6% for detection rate and 66.2% for FPR.
- 对所有分析，研究间的异质性很低,但高于13三体,使用I^2评估时21.6%的检出率和66.2%的假阳性率。

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Future perspectives展望

- Further studies are needed to evaluate performance of cfDNA testing in twin pregnancies
- 还需要进一步的研究来评估cfDNA测试在双胎妊娠的表现

Discussion points讨论要点

- Should cfDNA testing for fetal aneuploidies be introduced as routine screening for the whole population or only as contingent screening, based on abnormal first-line screening results?
- cfDNA测试胎儿非整倍体是否应该作为所有人群的常规筛查或只是当一线筛查结果异常时作为条件性筛查？

- Would it be appropriate to offer cfDNA screening for sex chromosome aneuploidies?
- 提供cfDNA筛查性染色体非整倍体是否合适？