胎儿常见染色体异常的筛查

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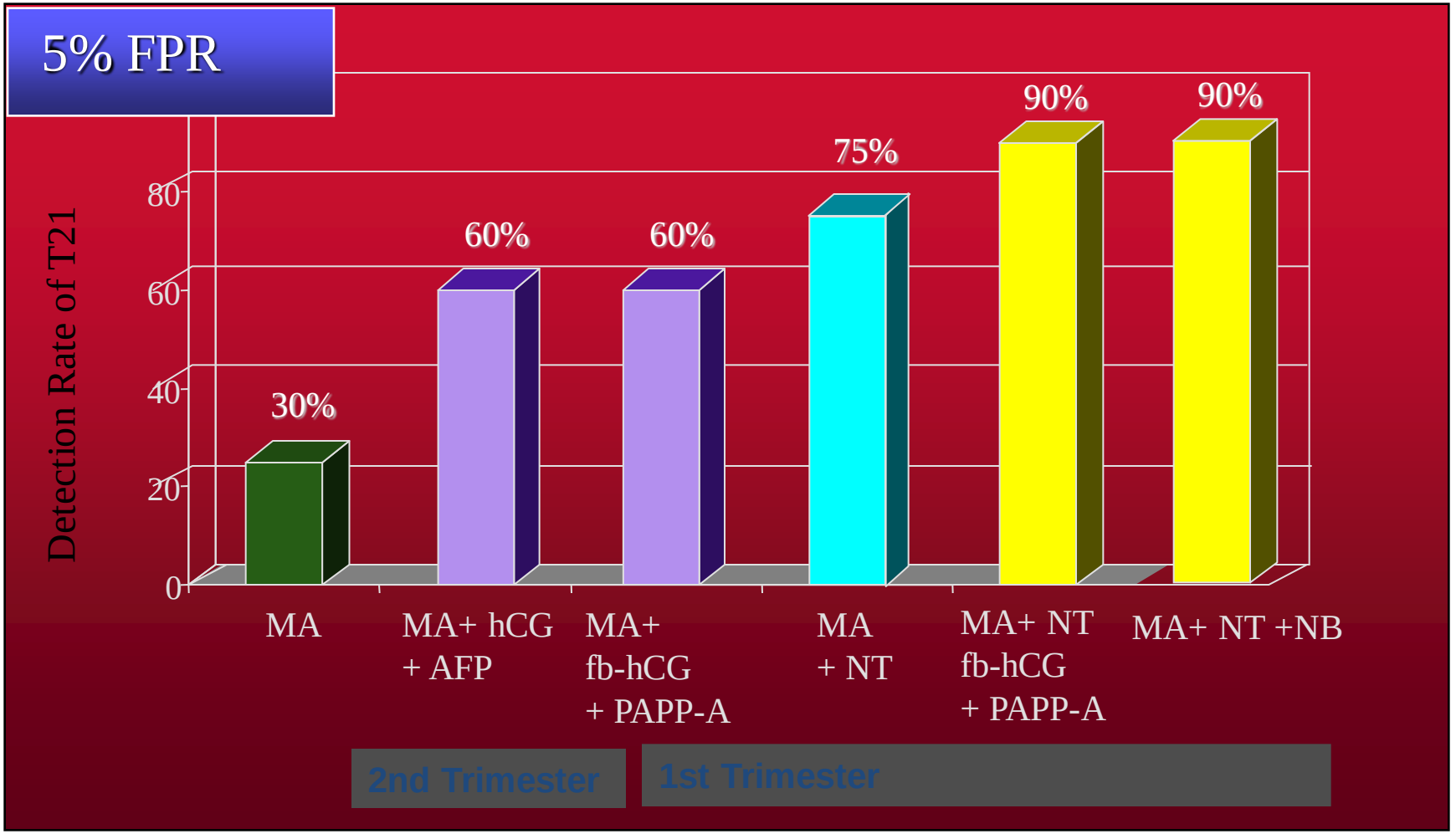
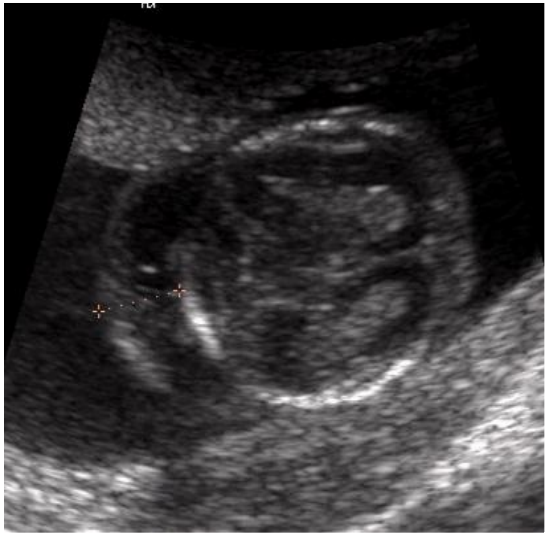


Bindra et al UOG 2002

胎儿常见染色体异常的超声特征

	21三体	18三体	13三体	Turner	三倍体
侧脑室扩大	+	+	—	+	—
前脑无裂畸形	—	—	+	—	—
脉络丛囊肿	+	+	—	—	—
后颅窝囊肿	+	+	+	—	—
后颅窝池扩大	+	+	+	—	—
小头畸形	—			—	+
唇裂	—	+		—	—
颈部水囊瘤	+	+	+	—	—
先天性心脏病		+	+		+
膈疝	—	+	+		—
十二指肠闭锁	+		—	—	—
小胃	+		—	—	—
肾盂积水	+		+	—	+
其他肾畸形	+	+	+		—
IUGR	+	+	—		+
股骨短	+	+	—	+	+
多指畸形	—	—	+	—	—

Second trimester sonographic markers of Down syndrome



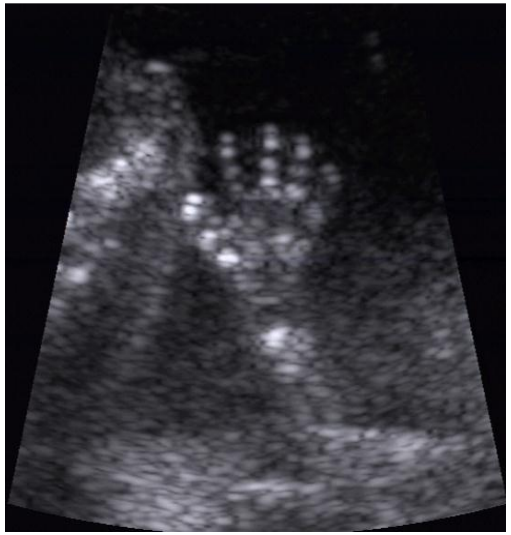
Nuchal Fold

Duodenal atresia

Pyelectasis

CPC

AV Canal

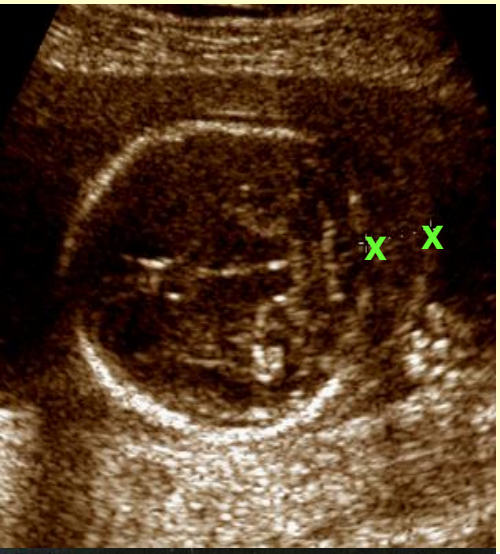


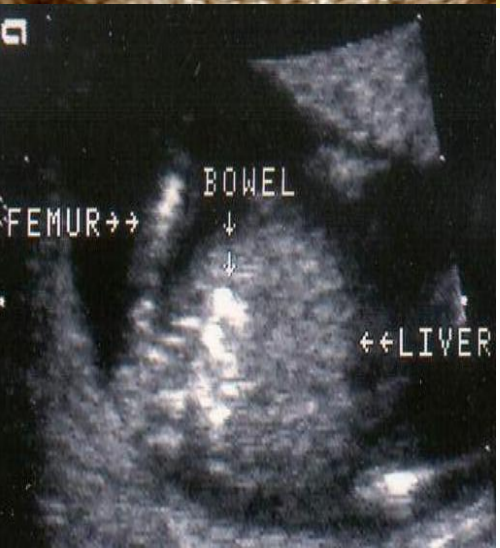
Clinodactyly

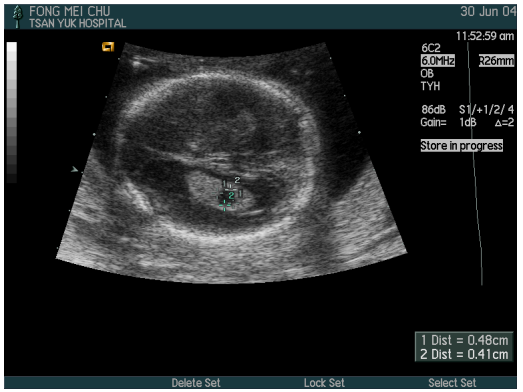
中孕期超声标志物 遗传超声

- Thickened nuchal fold,
  choroids plexus cyst,
  echogenic bowel,
  cardiac echogenic foci,
  single umbilical artery (SUA),
  persistent right umbilical vein,
  pyelectasis,
  short long bone,
  clinodactyly.

(Bromley et al., 2002, Nicolaides, 2003, Nyberg et al., 2001).







中孕期超声标志物

Major marker /hard marker

Minor /Soft marker

???

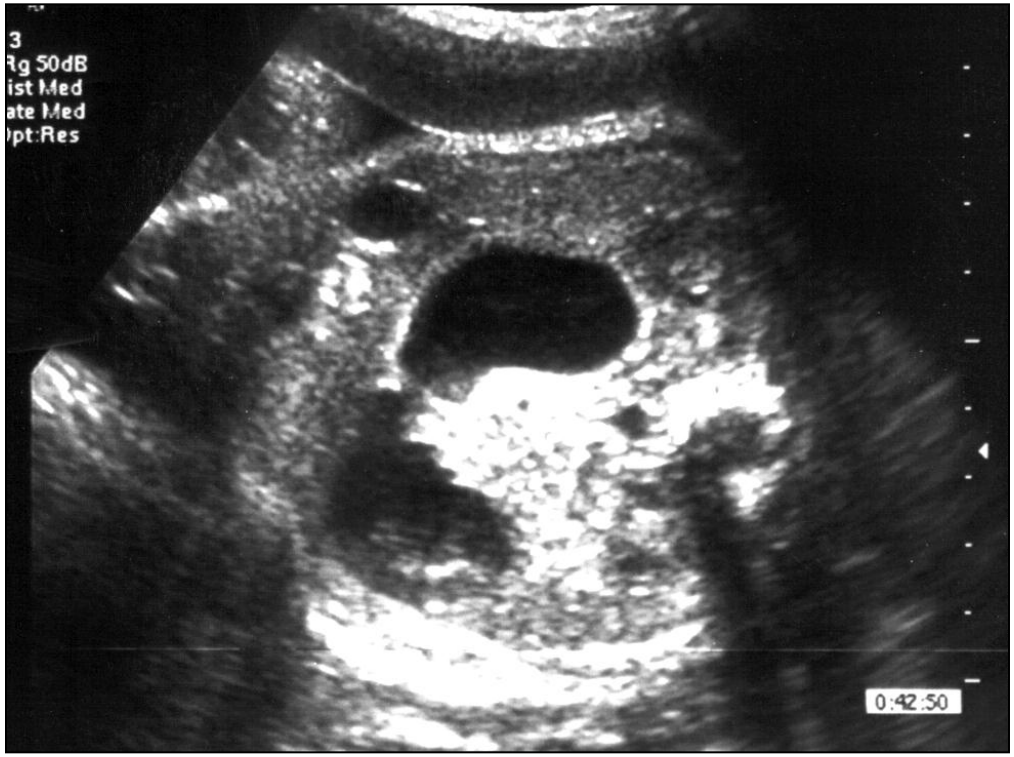
中孕期超声标志物

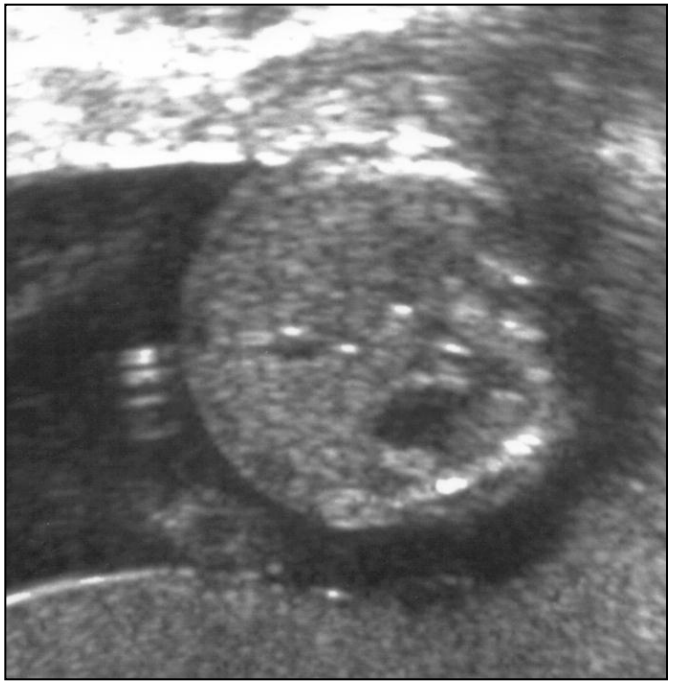
Major marker /hard marker 结构异常， 畸形

Minor /Soft marker

???

中孕期超声:结构异常

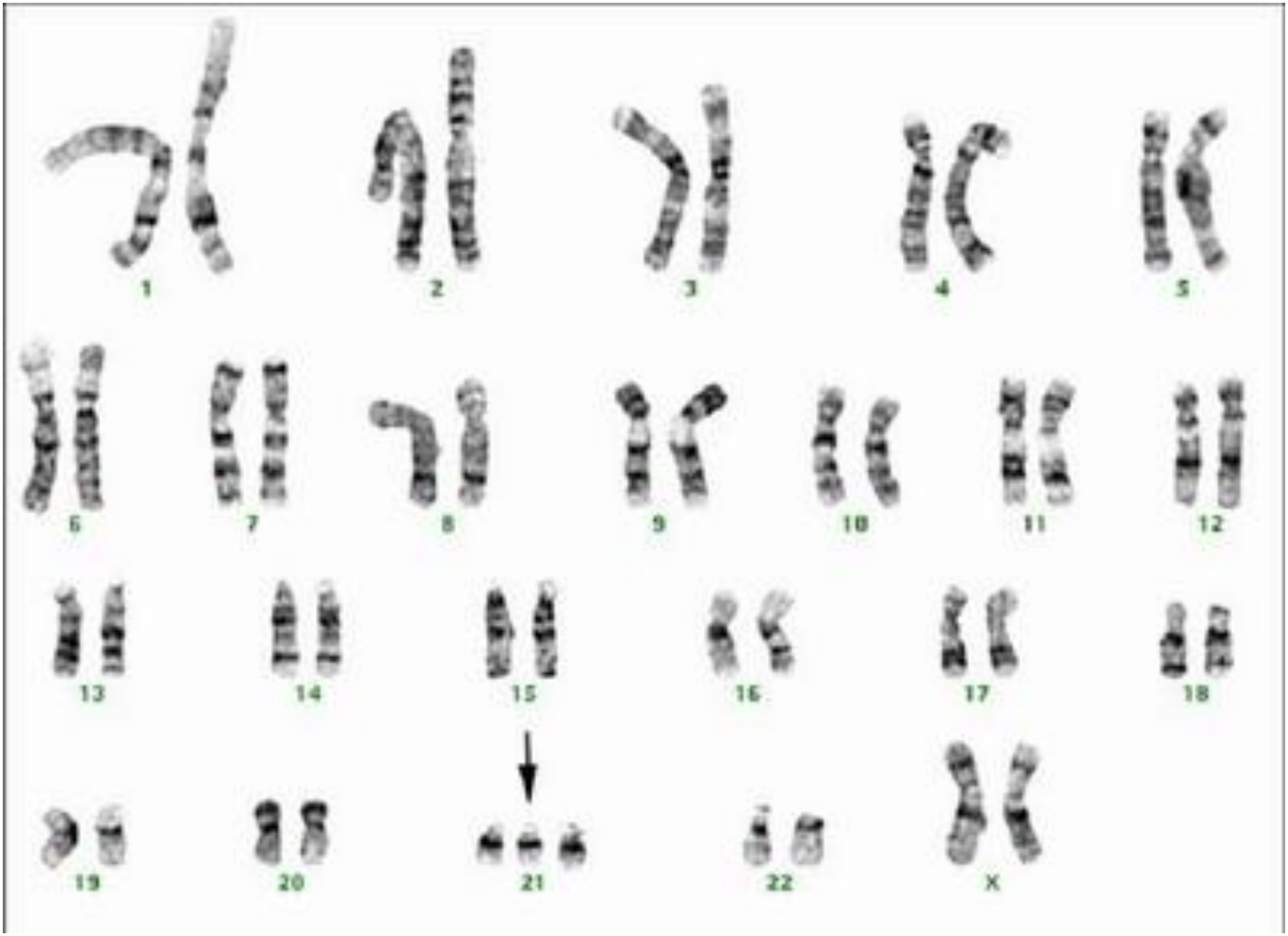




十二指肠闭鎖: 30%有21三体

中孕期超声:结构异常

房室间隔缺损：40%有21三体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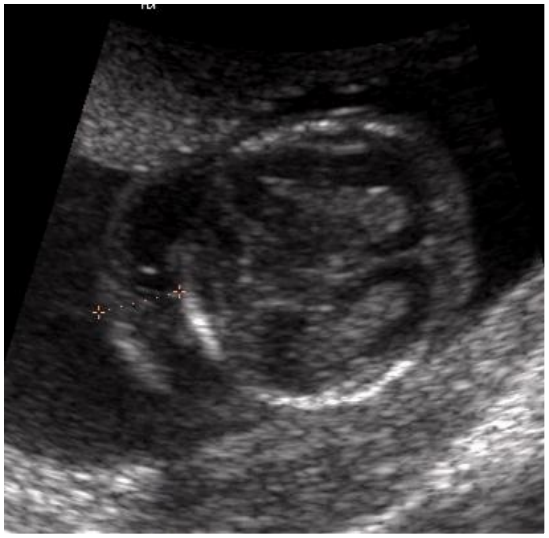
Second trimester sonographic markers of Down syndrome



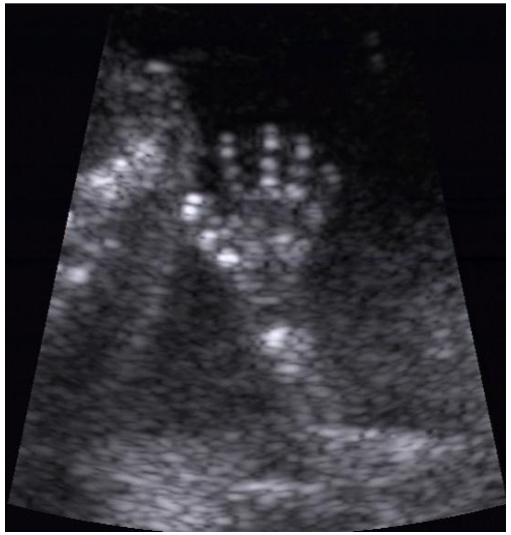
Nuchal Fold

Duodenal atresia

Pyelectasis

CPC

AV Canal

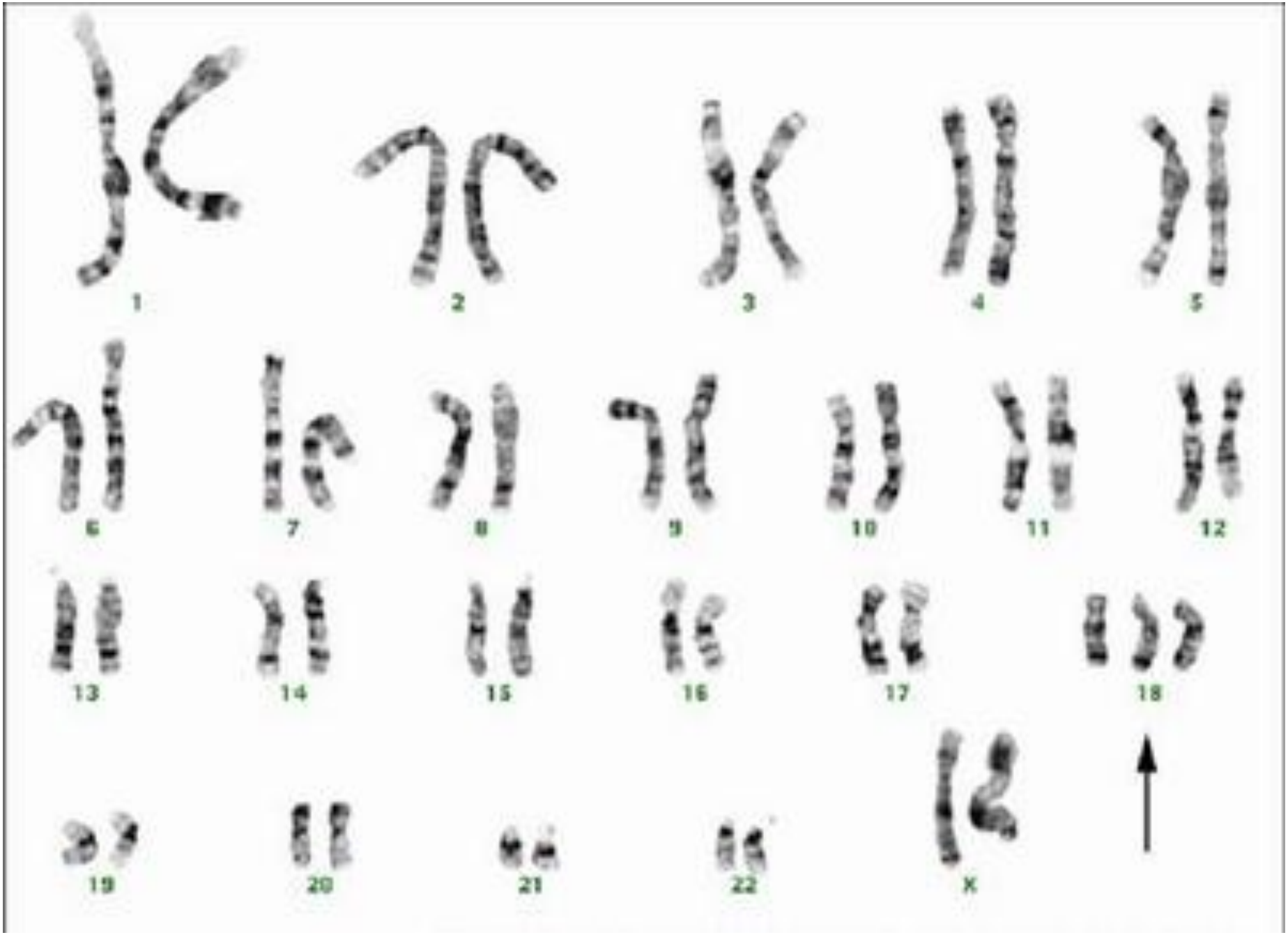


Clinodactyly

21三体中孕超声软标志物

- ❖鼻骨发育不全
- ❖颈皮增厚
- ❖心室内强回声点
- ❖肠管强回声
- ❖轻微肾盂扩张
- ❖股骨短小

- •肱骨短小
- •趾间间隔明显
- •小指内弯
- •小指骨发育不全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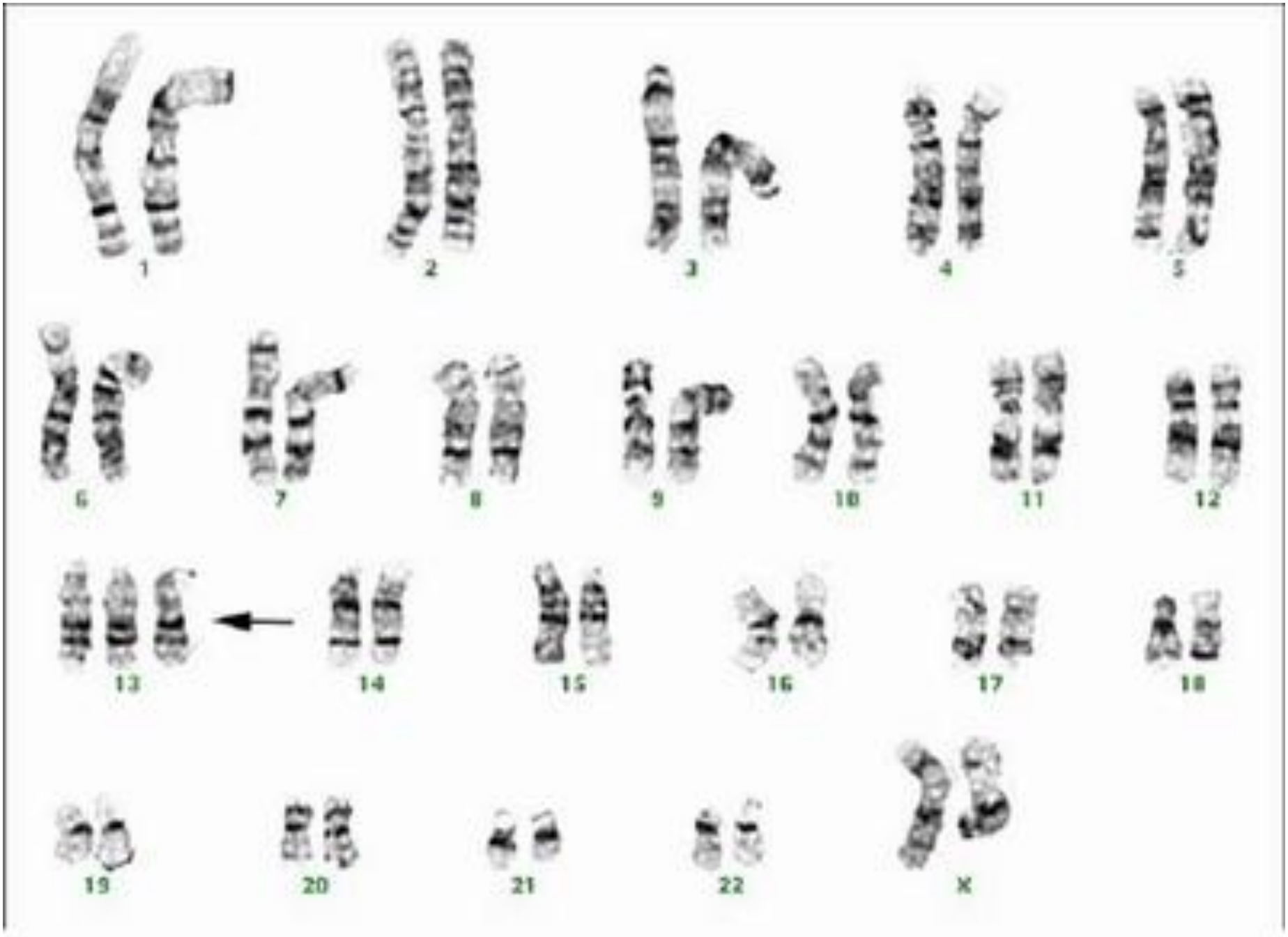
18三体中孕超声标志物

- ❖草莓头
- ❖脉络膜囊肿
- ❖胼胝体缺失
- ❖小脑延髓池增大
- ❖颜面裂
- ❖下颌过小
- ❖颈皮增厚

- •单脐动脉
- •生长迟缓
- •肢体短小
- •桡骨发育不全
- •手指交迭
- •内翻足
- •船底状脚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13三体中孕超声标志物

- 全前脑
- 小头症
- 脸部异常
- 心脏畸形
- 肾脏肿大或强回声
- 脐膨出
- 轴后多指症

中孕期超声标志物

Major marker /hard marker 结构异常， 畸形

- 与染色体异常的关系
- 如染色体正常:仍需治疗
- 预后

中孕期超声:软标志物
(Soft Markers)

They are of interest because of their statistical association with chromosomal aberrations, an association that makes them potential identifiers of these conditions.

Nicolaides et al 1992

中孕期超声:软标志物
(Soft Markers)

特殊的超声特征:

非特异性

短暂的

没有病理意义

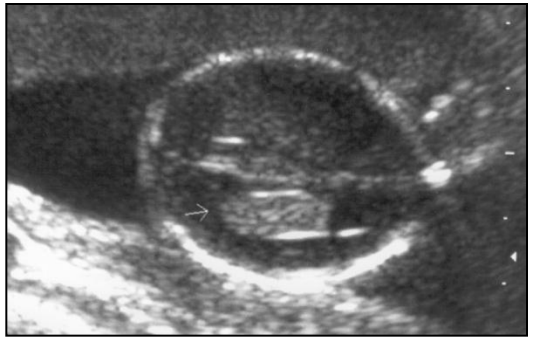
但与染色体异常相关=潜在预测力?

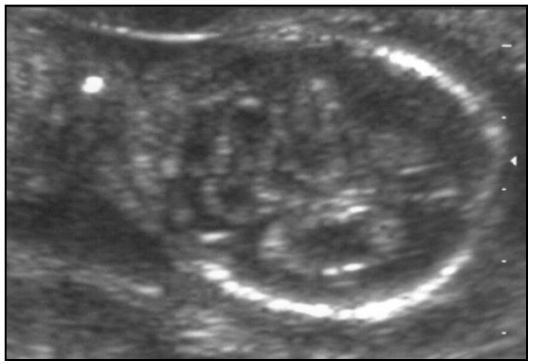
如果后来研究发现这种预测力太弱，是无用的，软标志物将不再有临床意义，应该被扔进垃圾桶。

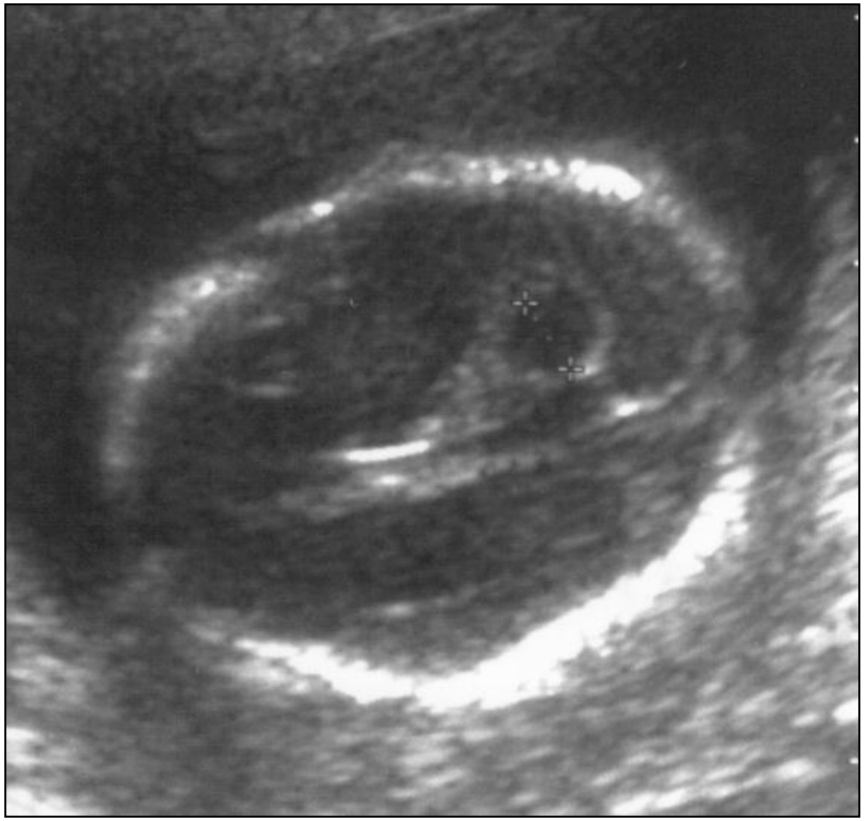
Soft markers

- 轻微肾盂扩张
- 脉络膜囊肿
- 心室内强回声点
- 肠管强回声
- 颈皮增厚
- 胎儿鼻骨发育不全 / 缺失

中孕期超声:软标志物





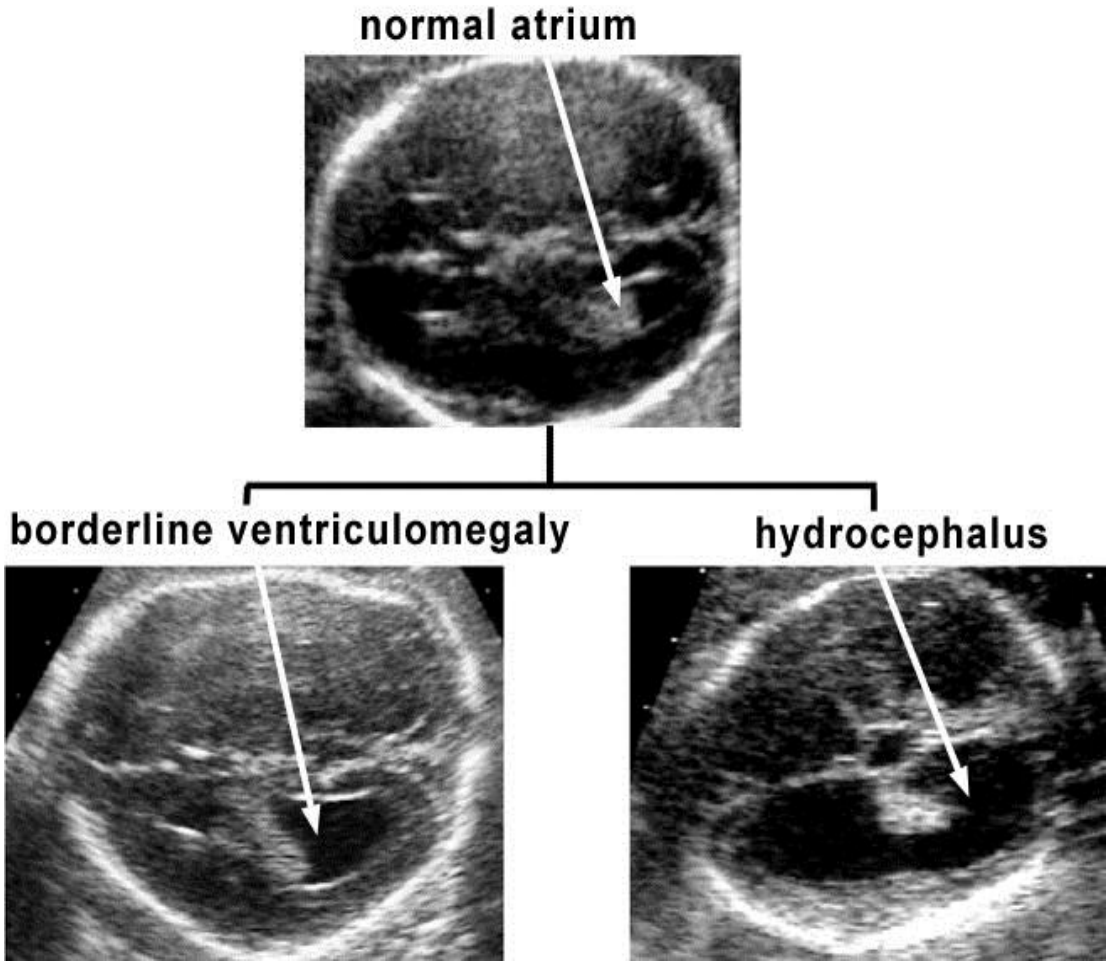


脉络膜囊肿 (Choroid Plexus Cysts CPC)

中孕期超声:软标志物（1）

颈皮增厚

中孕期超声:软标志物（2）



轻度脑室增宽

Ultrasound Obstet Gynecol 2009; 34: 212–224
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/uog.7307

Counseling in isolated mild fetal ventriculomegaly

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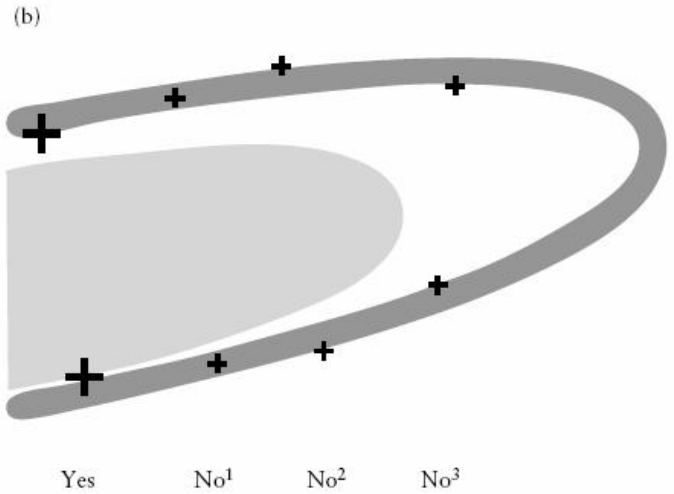
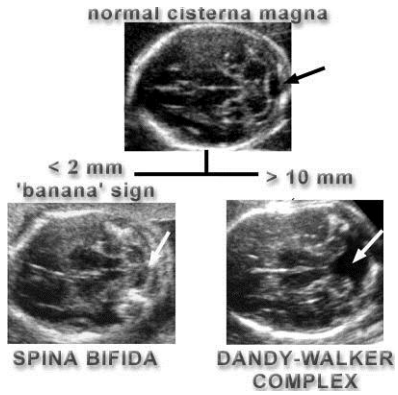
KEYWORDS: management; outcome; ultrasound; ventriculomegaly

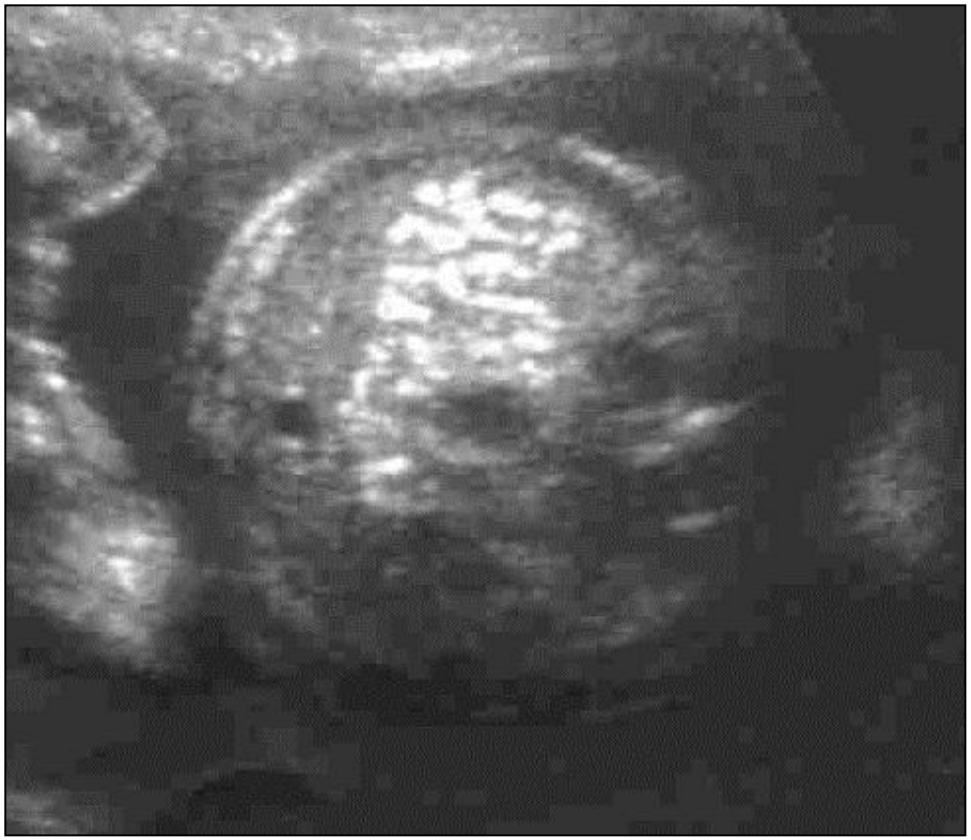


中孕期超声:软标志物（3）



后颅窝池增宽

中孕期超声:软标志物（4）



肠管强回声

中孕期超声:软标志物（5）

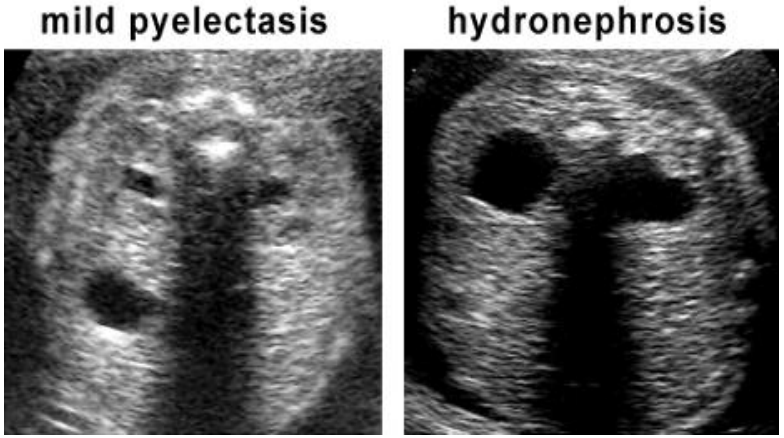
心室内强回声点

- 与胎儿染色体异常的关系：
  - 左心室单发局灶性强回声较常见，胎儿染色体异常发生的可能性仅为0-1.8。而右心室、双心室多发或明显的灶状强回声胎儿染色体异常的危险性增高，有条件应行胎儿染色体组型分析。

中孕期超声:软标志物（6）

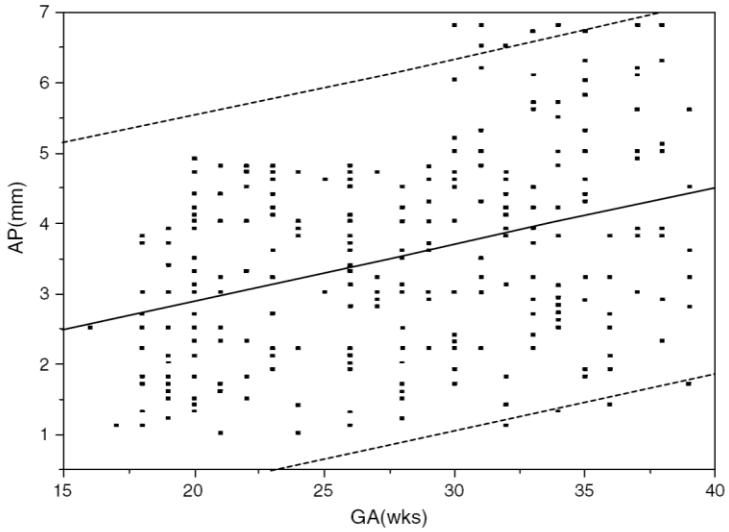
轻微肾盂扩张

肾盂扩张 -- 肾盂积水



- 肾盂扩张 （肾盂分离）
  - 前后径随孕周增加
  - 肾盂前后径存在变异
  - 没有一致的标准
    - 18 - 23周: ≥ 5mm
- 肾盂积水 ≥10 mm
  - 尿路病变
- 肾盂积水 ≥ 20 mm
  - 尿路病变，需要手术

Natural history of fetal hydronephrosis diagnosed on mid-trimester ultrasound. Ultrasound Obstet Gynecol. 2001 Mar;17(3):191-6.



中孕期超声标志物的问题

- 定义的不同
- 筛查时间不同
- 低危 / 高危人群
- 与其他标志物间之互相影响
- 是独立的还是多种的标志物
- 人种的影响
- 其他筛查的影响

21三体中孕超声标志物

Table 3. Comparison of Fetuses With Down Syndrome and Controls for Both Sonographic Markers and Major Abnormalities (With or Without Markers)

No. of Markers	*Down Syndrome (n=186)*	*Controls (N=8712)*	*Likelihood Ratio**
0	31.2% (58)	86.7% (7541)	0.36
1	22.6% (42)	11.3% (987)	2.0
2	15% (28)	1.5% (136)	9.6
3+	14.5% (27)	0.1% (11)	115
Major abnormality with or without marker	16.7% (31)	0.4% (37)	39.2

* Percent of Down syndrome cases/controls.
Data from ref 13.

Nyberg 2003. Seminar Perinatology

中孕超声标志物的处理

- 0 或1个标志物: 低危
- 2 个或以上标志物: 高危
- 孕妇年龄也算是一個标志物

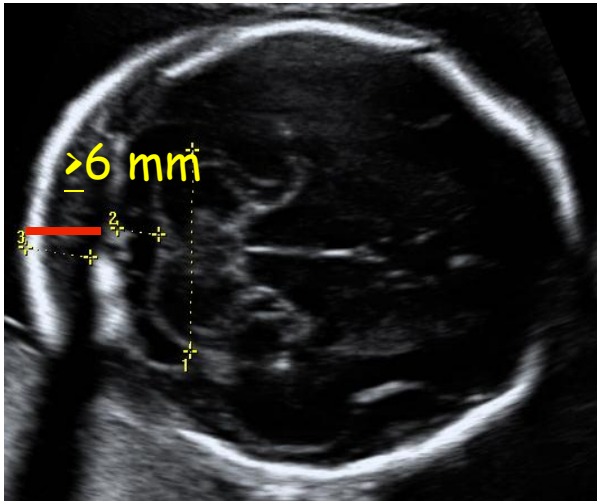
中孕超声标志物风险计算

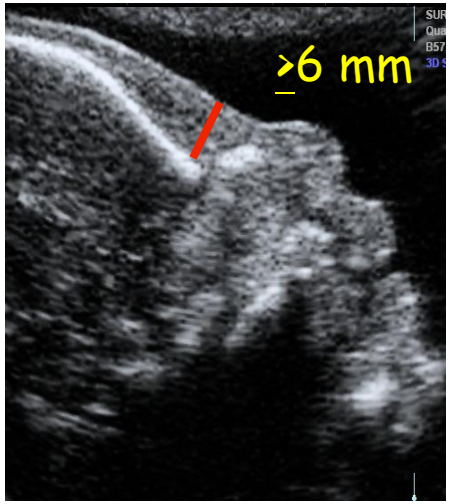
	似然比
肾盂扩张	1.0-1.5x
脉络膜囊肿	1.0-1.55x
心室内强回声点	1.0-1.5x
肠管强回声	3.0x
颈皮增厚> 6 mm	6.0-10x
胎儿鼻骨发育不全 / 缺失	> 20x

21三体标志物的似然比

About 1: 脉络膜囊肿,肠管强回声,肾盂扩张,股骨短小

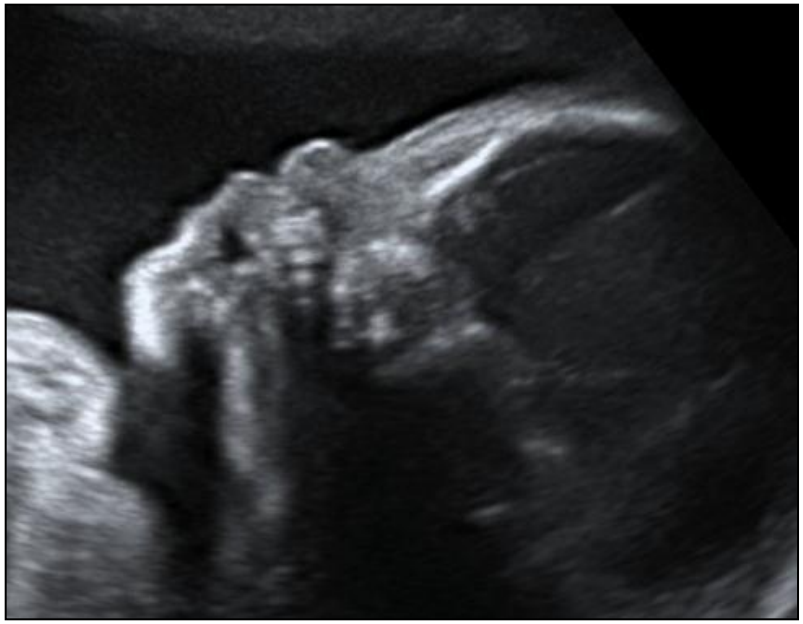
About 10: 颈皮增厚 **or** 鼻前皮肤增厚 **and** 鼻骨发育不全





NB <5 mm

胎儿鼻骨 (NB) 发育不全 / 缺失



胎儿鼻骨 (NB) 发育不全

Sonek JD & Nicolaides K. AJOG 2002

Table 1 Normal ranges for nasal bone lengths (in millimeters) ($n = 3537$)

Gestational age (weeks)	*Subjects* (n)	*Percentile*				
		2.5%	*5%*	*50%*	*95%*	*97.5%*
11	16	1.3	1.4	2.3	3.3	3.4
12	54	1.7	1.8	2.8	4.2	4.3
13	59	2.2	2.3	3.1	4.6	4.8
14	82	2.2	2.5	3.8	5.3	5.7
15	103	2.8	3.0	4.3	5.7	6.0
16	134	3.2	3.4	4.7	6.2	6.2
17	203	3.7	4.0	5.3	6.6	6.9
18	252	4.0	4.3	5.7	7.0	7.3
19	388	4.6	5.0	6.3	7.9	8.2
20	440	5.0	5.2	6.7	8.3	8.6
21	322	5.1	5.6	7.1	9.0	9.3
22	208	5.6	5.8	7.5	9.3	10.2
23	157	6.0	6.4	7.9	9.6	9.9
24	121	6.6	6.8	8.3	10.0	10.3
25	123	6.3	6.5	8.5	10.7	10.8
26	96	6.8	7.4	8.9	10.9	11.3
27	80	7.0	7.5	9.2	11.3	11.6
28	103	7.2	7.6	9.8	12.1	13.4
29	95	7.2	7.7	9.8	11.8	12.3
30	104	7.3	7.9	10.0	12.6	13.2
31	92	7.9	8.2	10.4	12.6	13.2
32	66	8.1	8.6	10.5	13.6	13.7
33	54	8.6	8.7	10.8	12.8	13.0
34	41	9.0	9.1	10.9	12.8	13.5
35	37	7.5	8.5	11.0	14.1	15.0
36	40	7.3	7.8	10.8	12.8	13.6
37	36	8.4	8.7	11.4	14.5	15.0
38	13	9.2	9.3	11.7	15.7	16.6
39	12	9.1	9.2	10.9	14.0	14.8
40	6	10.3	10.4	12.1	14.5	14.7

Sonet et al 2003

中国人种

Table 1—Length of nasal bone (mm) in second trimester

Gestational age (weeks)	Cases	5% centile	Median		95% centile
15–15 + 6	3	3.2	3.5	4.3	3.9
16–16 + 6	35	3.3	4.1	4.7	5.0
17–17 + 6	72	3.9	4.6	5.3	5.4
18–18 + 6	43	4.3	5.0	5.7	5.9
19–19 + 6	21	4.3	5.6	6.3	6.8
20–20 + 6	12	5.5	5.8	6.7	6.7
21–21 + 6	7	5.0	6.2	7.1	7.5
22–23	5	6.2	6.7	7.5	8.1
Total	198				

Chen M et al. Prenat Diagn 2004

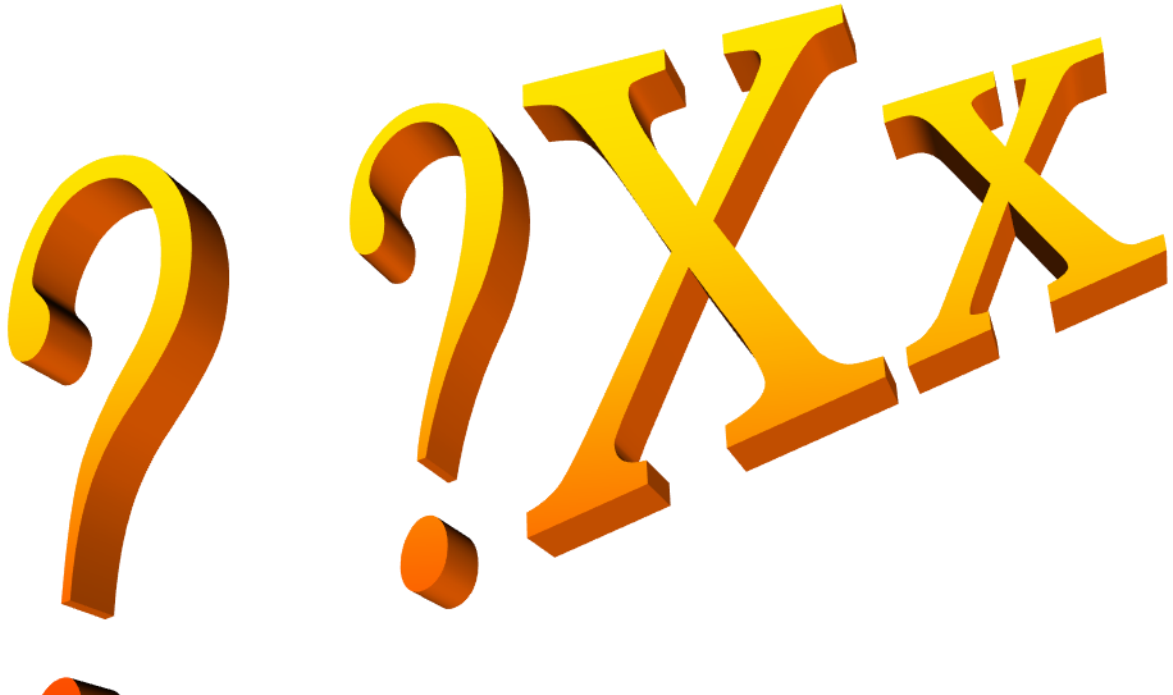
胎儿鼻骨 (NB) 发育不全 / 缺失是最强的软标志物

发育不全的定义

- Bromley et al 2002: BPD/NB 比率
  - >=9: DR 100%, FPR: 22%
  - >=10: DR 81%, FPR: 11%
  - >=11: DR 69%, FPR: 5%
- Gianferrari et al 2007: MoM
  - <0.80MoM: DR 95.2%, FPR 7.4%
  - <0.75MoM: DR 85.7%, FPR:2.9%
- <2.5th 百分位数
- <5th 百分位数
- <2.5mm

如何建立解决的方案

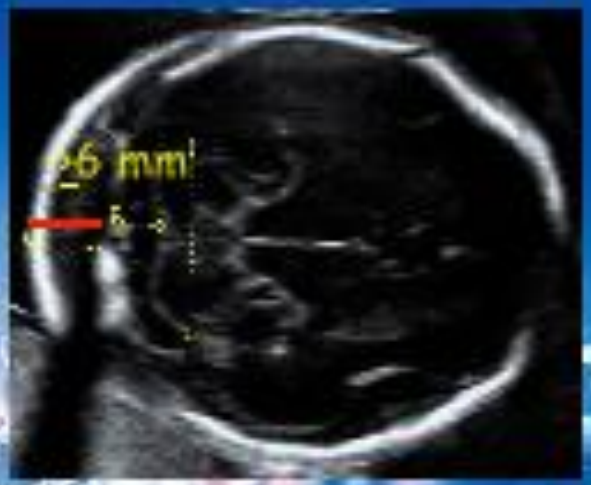
- 建立自己的LR
  或者建立国人的LR，从目前众多的软指标中选取对自己有用的软指标



21三体标志物的似然比

About 1: 脉络膜囊肿,肠管强回声,**肾盂扩张**,股骨短小

About 10: 颈皮增厚 **or** 鼻前皮肤增厚 **and** 鼻骨发育不全



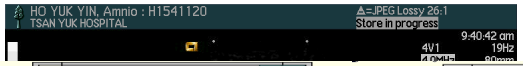
NB <5 mm

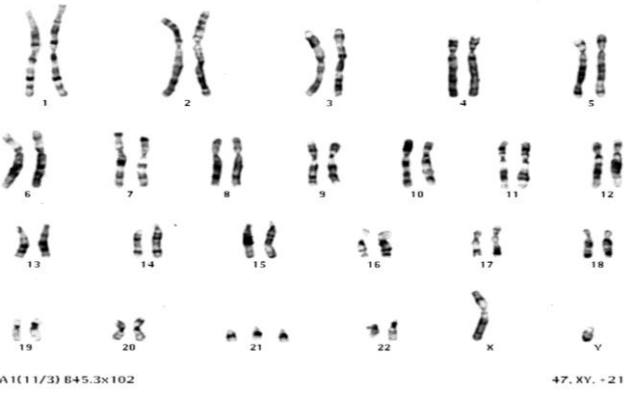
香港中文大學
The Chinese University of Hong Kong

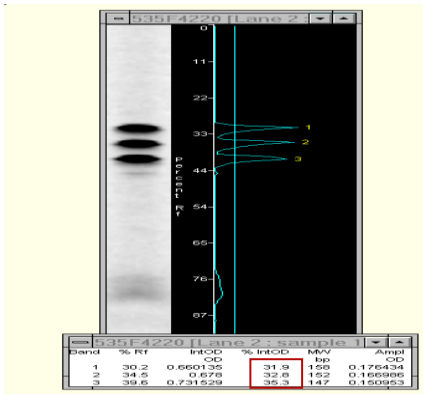
USG 只是一个工具

? :

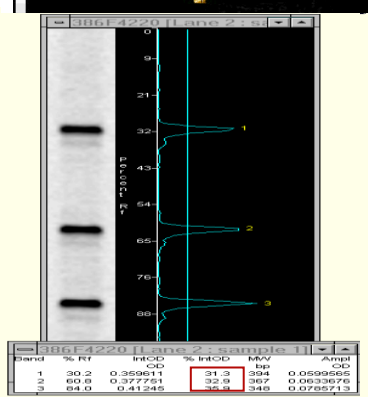
?







1 : 1 : 1



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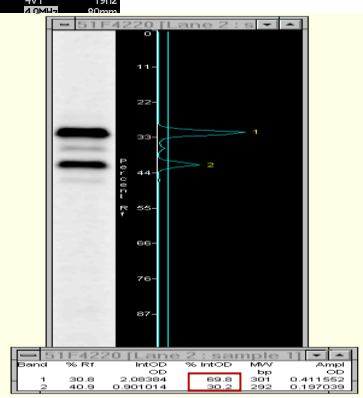
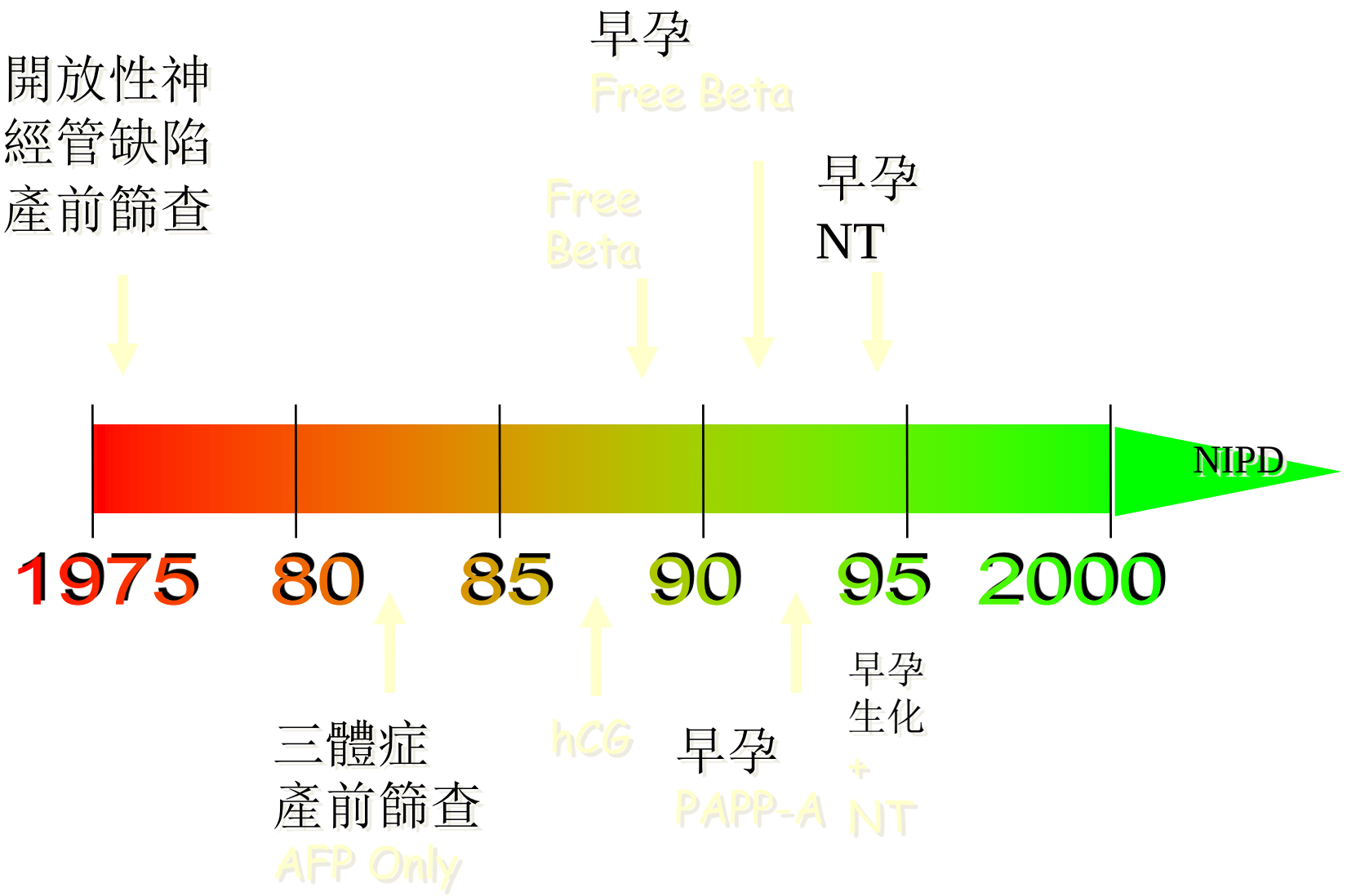
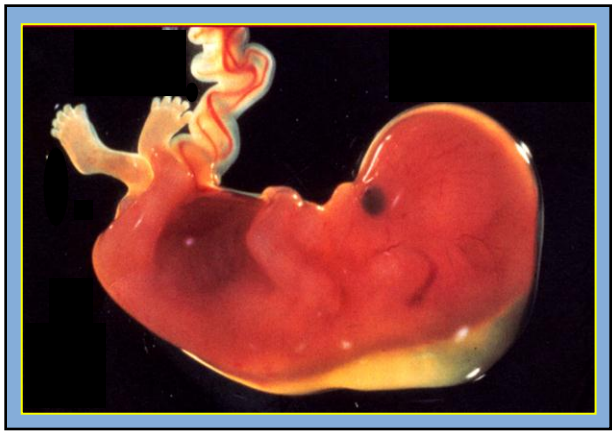


2 : 1

Prenatal Screening



21 三体的筛查

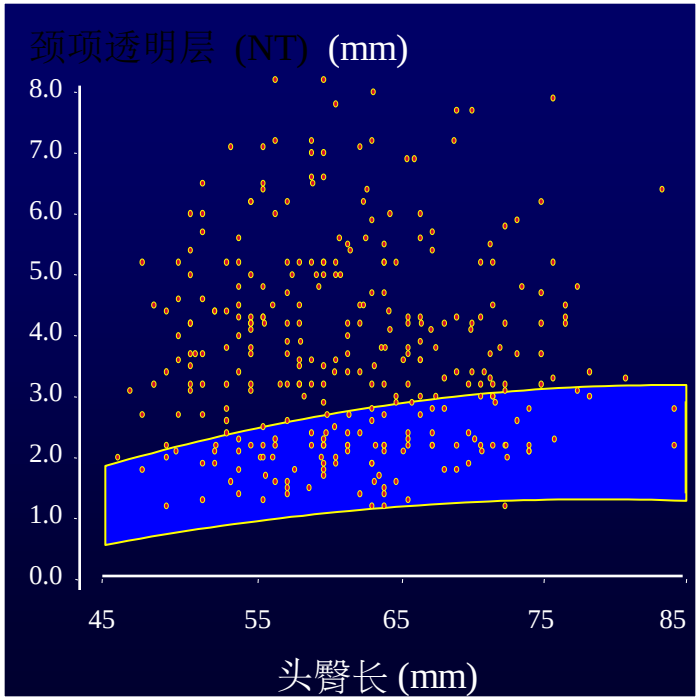


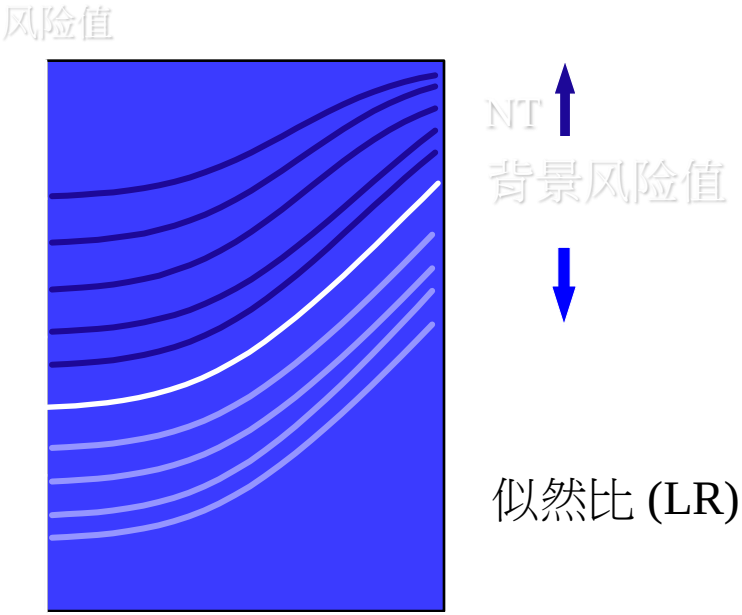
‘ The skin is deficient in elasticity giving the appearance of being too large for the body……. The face is flat and the nose is small. ’

Langdon Down (1866) Observations on an ethnic classification of idiots

21 三体的筛查

颈项透明层





- 正常的胎儿，其NT大小与孕周成正比
- 21三体的胎儿，其NT比正常的胎儿厚（75%以上的病例，其NT在第95百分位以上）
- 胎儿患有21三体的背景风险值，与NT推算出来的似然比(LR)相乘，便可计算出此胎儿患有21三体的风险值
- 胎儿的NT值与正常NT中位数的相差愈大，LR愈大

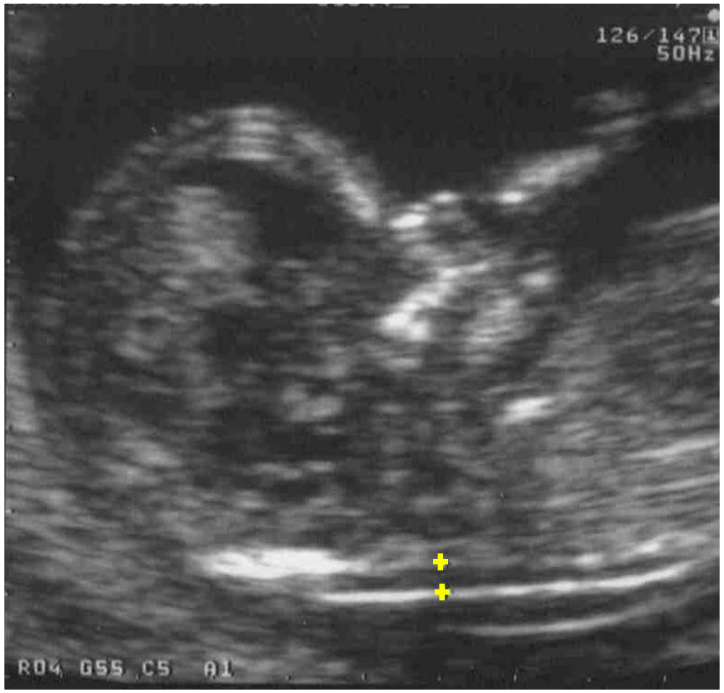
Snijders et al, Lancet 1998;351:343–6.

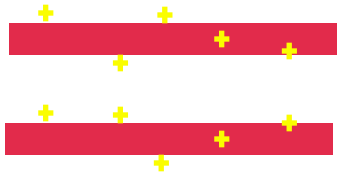
风险评估

Risk = Background risk * LR_{NT} * LR_{PAPP-A} * $LR_{f\beta-hCG}$

1. 孕妇年龄
2. 妊娠期
3. 三体症胎儿怀孕史

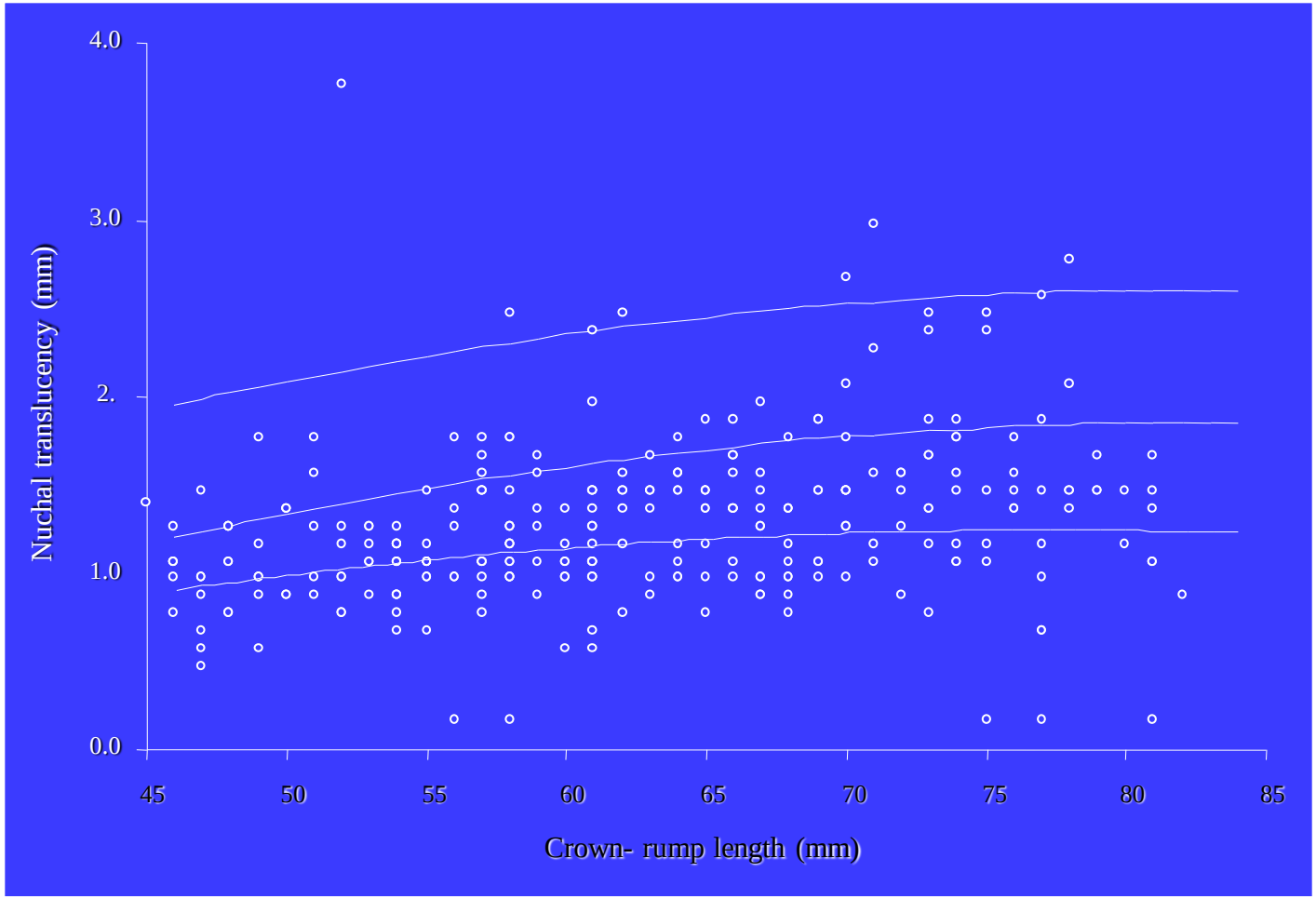
颈项透明层





- 11-13+6周
- 头臀长为45-84 mm
- 正中矢切面图
- 尽可能放大：轻微移动游标尺 0.1 mm
- 颈部在自然姿势
- 分辨羊膜
- 最阔的透明地带量度
- 游标尺 *on the line*

颈项透明层审计 - *FMF audit*



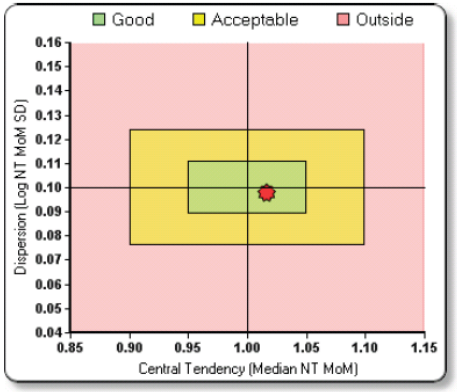
Monitoring Quality – Quantitative

Central Tendency and Dispersion Assessment

Average

Period	Median	Log10 SD
May 2010 to Apr 2011	1.02	0.0981

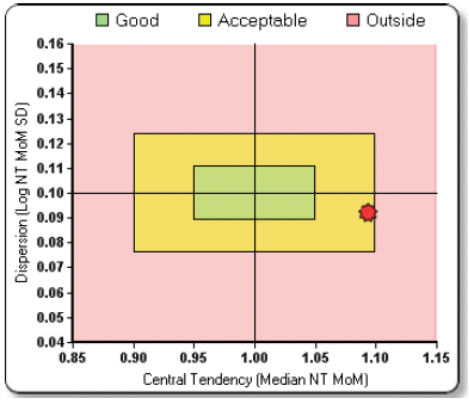
- Annual Median: Within expectations



Over

Period	Median	Log10 SD
May 2010 to Apr 2011	1.09	0.0922

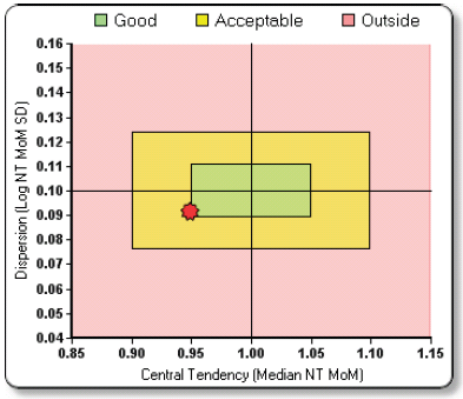
- Annual Median: Acceptable but monitoring required



Under

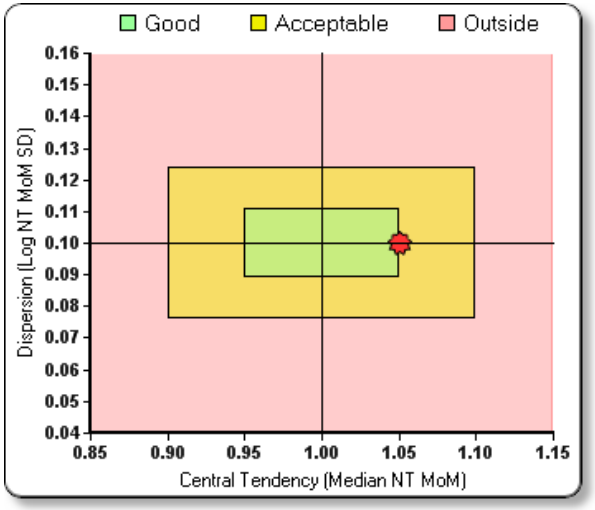
Period	Median	Log10 SD
May 2010 to Apr 2011	0.95	0.0916

- 0.9 < Annual Median: Acceptable but monitoring required

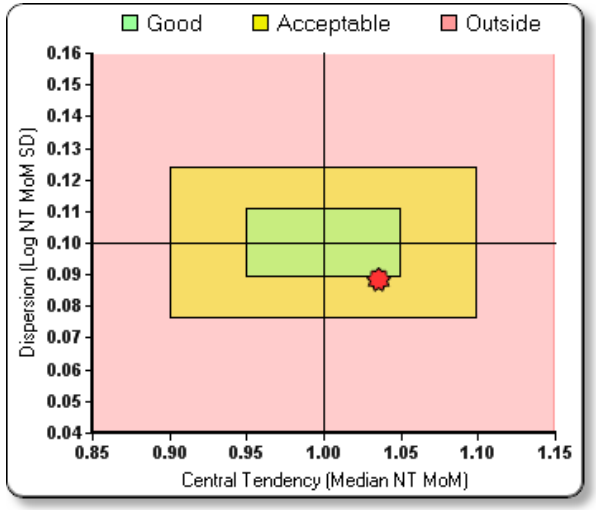


Monitoring Quality – CUSUM

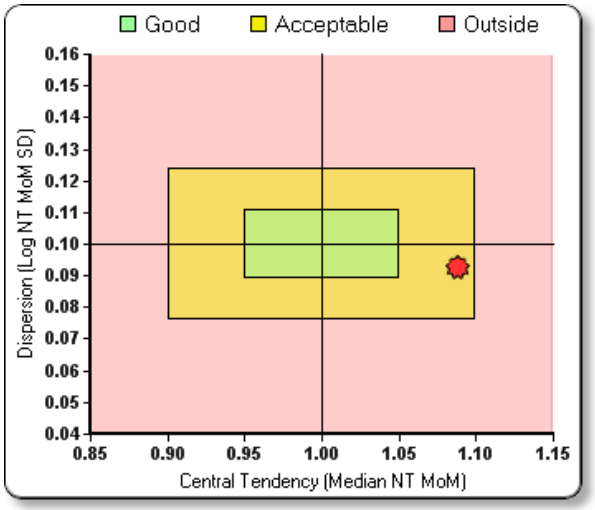
Centre A



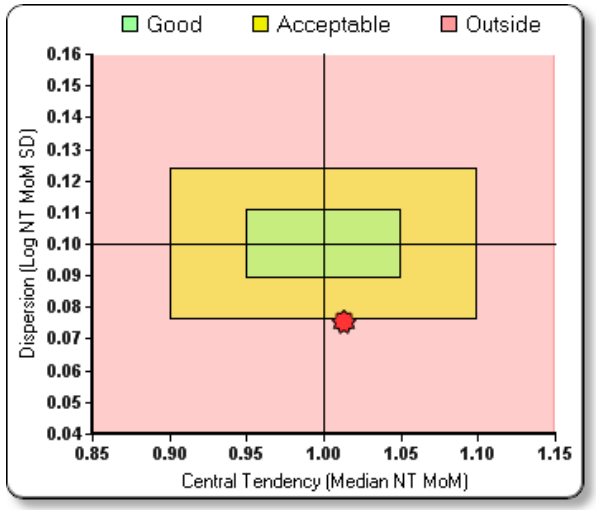
Centre B



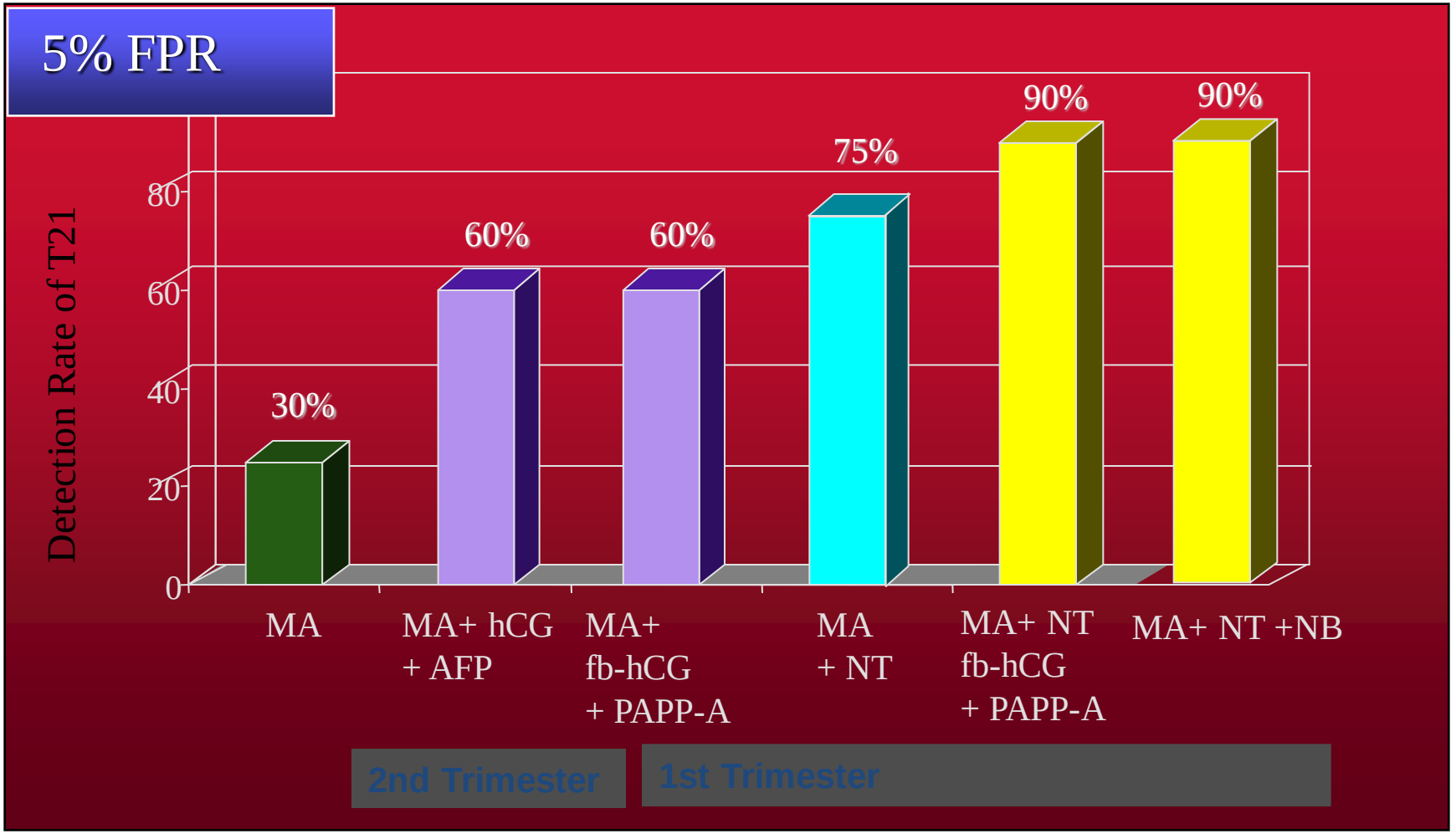
Centre C



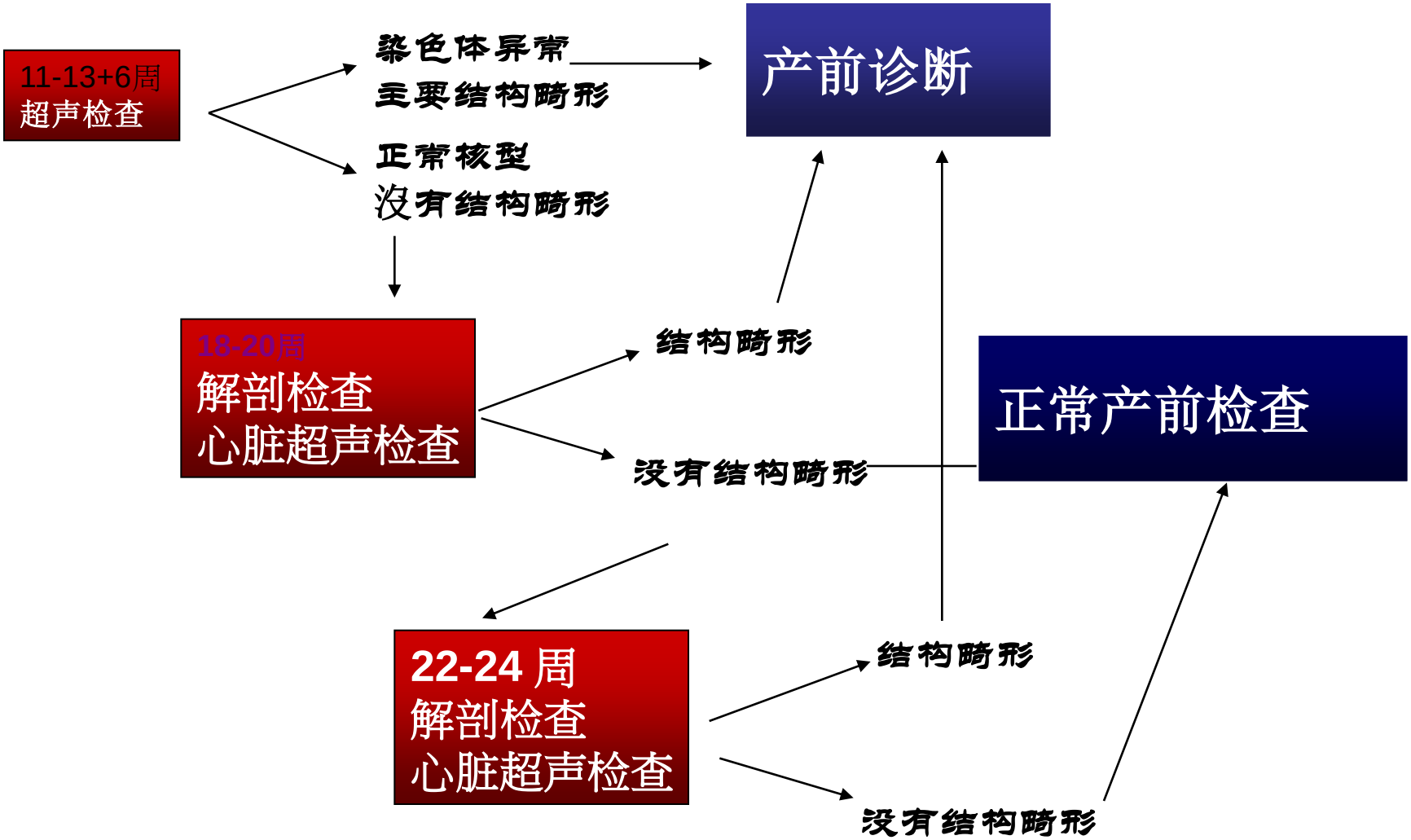
Centre D



早孕期（妊娠11-13+6周时）筛查



Bindra et al UOG 2002


11-13+6周
超声检查
染色体异常
主要结构畸形
正常核型
没有结构畸形
产前诊断
18-20周
解剖检查
心脏超声检查
结构畸形
没有结构畸形
正常产前检查
22-24 周
解剖检查
心脏超声检查
结构畸形
没有结构畸形

细胞外游离的胎儿核酸

- **Clinical utility of noninvasive fetal trisomy (NIFTY) test - early experience.**
  无创性产前诊断：从梦想到现实

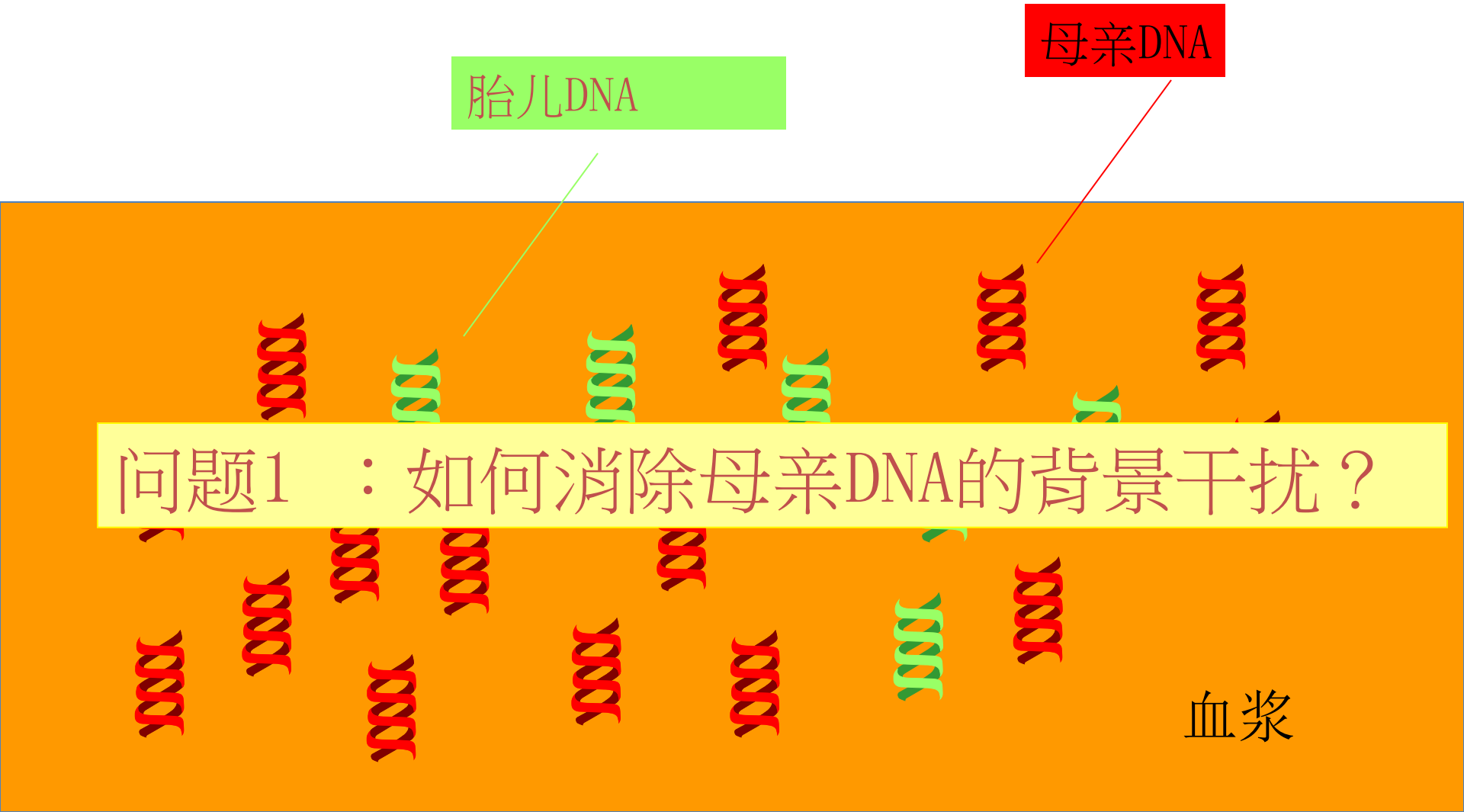
产前诊断中的应用

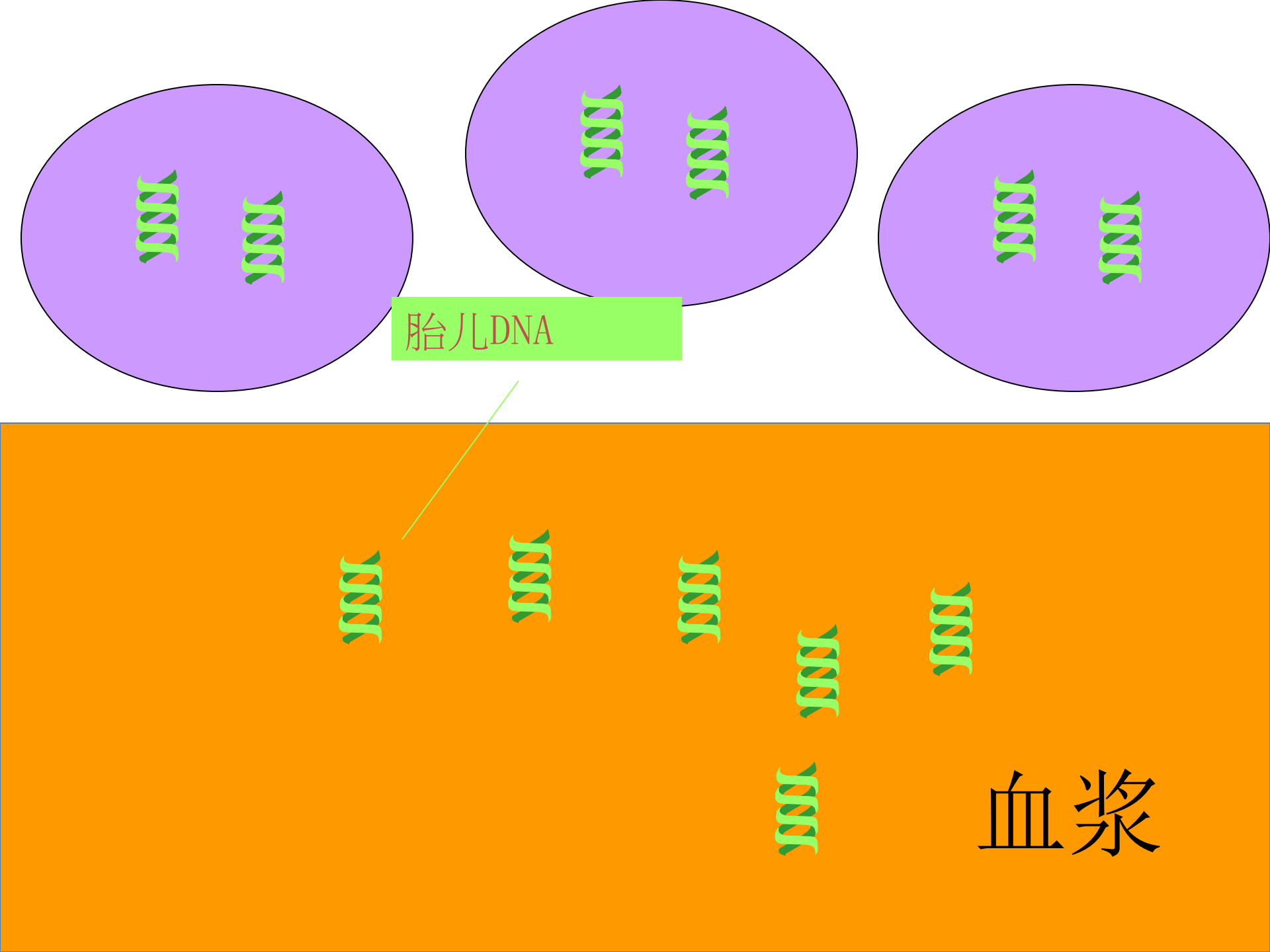
- 性连锁疾病胎儿性别鉴定
- **RhD**疾病**的**血型鉴定
- 父母遗传的常染色体显性遗传疾病

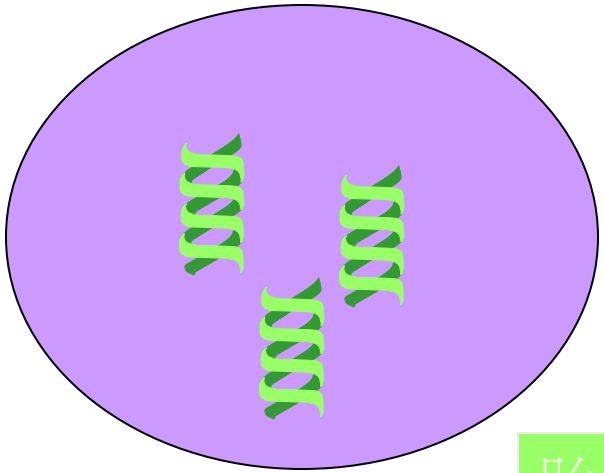
染色体非整倍体

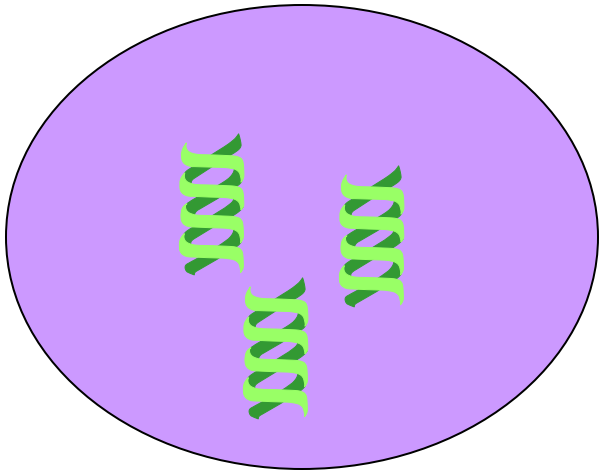
- 不是质量区别的问题
- 相对的数量/剂量的问题

染色体非整倍体




胎儿DNA
血浆





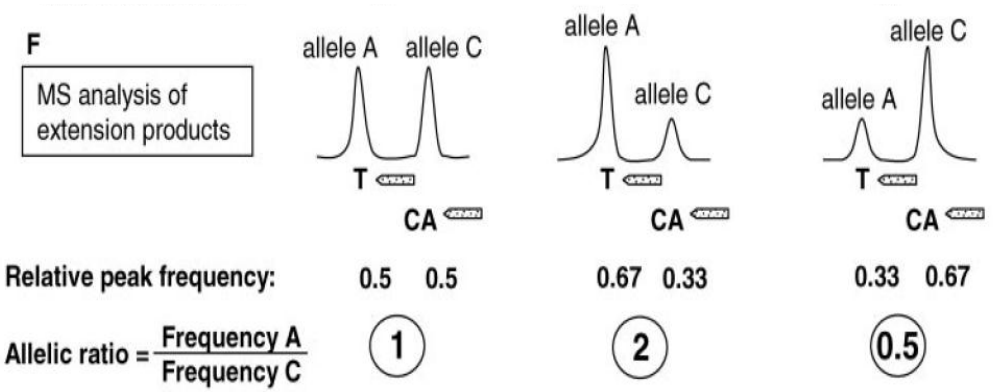
胎儿DNA

问题2 ：如何用细胞外的核酸预测胎儿细胞内21号染色体的数目？

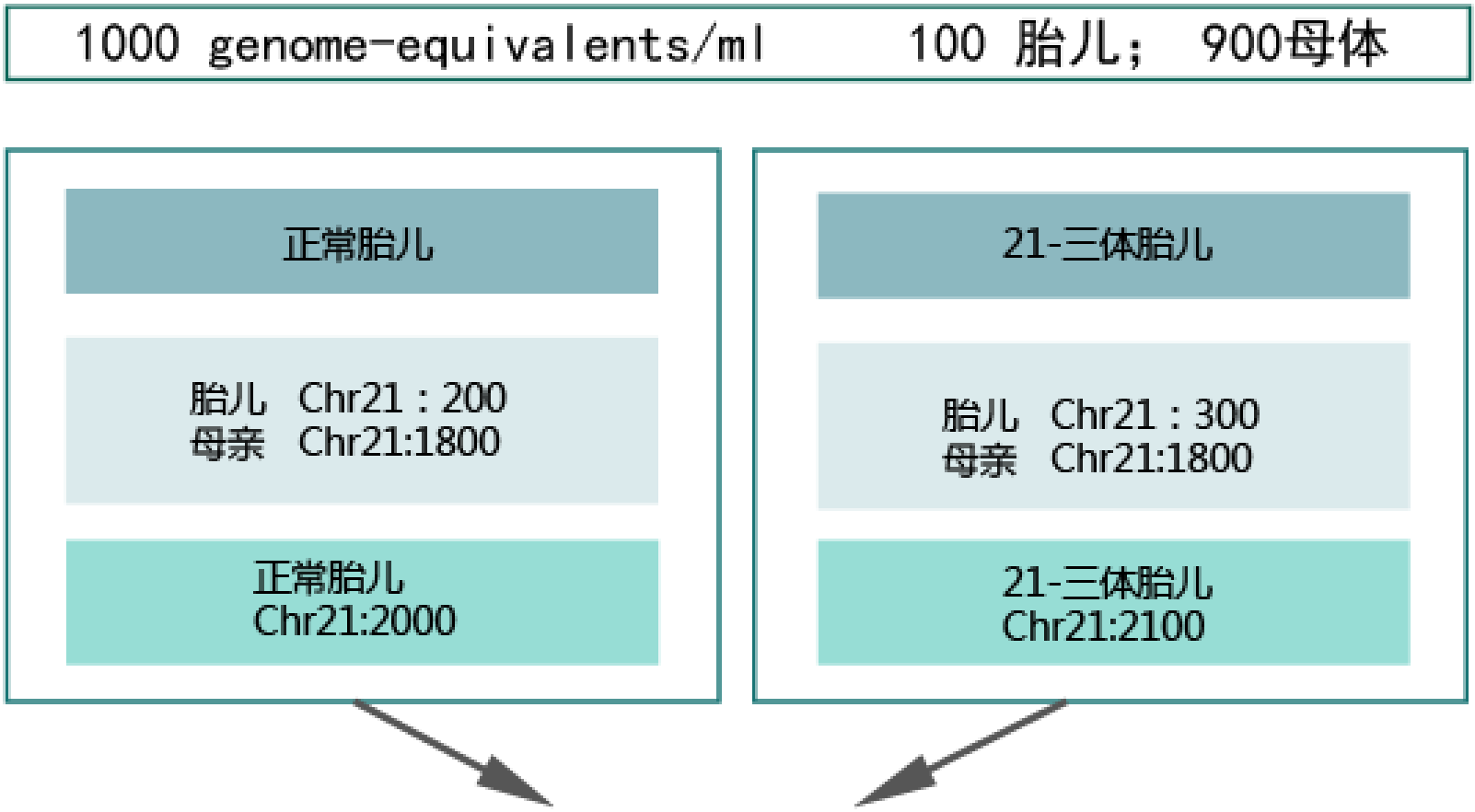
血浆

染色体非整倍体

- 胎儿特异性核酸
  - DNA甲基化差异
  - 胎儿特异性 RNA
- 多态性
  - 表观遗传学等位基因比例（ EAR ）
  - RNA的单核苷酸多态性比例
  - 正常1:1 ，三体 2:1 或1:2



无创性产前诊断的技术原理



TECHNICAL REPORTS

nature medicine

VOLUME 13 | NUMBER 2 | FEBRUARY 2007

Plasma placental RNA allelic ratio permits noninvasive prenatal chromosomal aneuploidy detection

Y M Dennis Lo[1,2,7], Nancy B Y Tsui[2,7], Rossa W K Chiu[1,2,7], Tze K Lau[3], Tse N Leung[3], Macy M S Heung[2], Ageliki Gerovassili[4], Yongjie Jin[5], Kypros H Nicolaides[4], Charles R Cantor[6] & Chunming Ding[1,5,7]

Clinical Chemistry 52:12
2194–2202 (2006)

Molecular Diagnostics and Genetics

Noninvasive Prenatal Detection of Fetal Trisomy 18 by Epigenetic Allelic Ratio Analysis in Maternal Plasma: Theoretical and Empirical Considerations

Yu K. Tong,[1] Chunming Ding,[2,3] Rossa W.K. Chiu,[1,3] Ageliki Gerovassili,[4] Stephen S.C. Chim,[5] Tak Y. Leung,[5] Tse N. Leung,[5] Tze K. Lau,[5] Kypros H. Nicolaides,[4] and Y.M. Dennis Lo[1,3*]

唐氏综合征筛查及诊断方法

	筛查率	假阳性率	限制性
早孕期（胎儿超声及母体血清）	90%	10%	孕11-13+6周进行
中孕期（母体血清）	65%	35%	孕14-20+6周进行
无创性（母体血清）	>99%	<1%	孕12周后进行
侵入性（绒毛活检术、羊水/脐血穿刺术）	100%	0	侵入性，0.5-1%流产率

NIFTY

- 取代soft marker
  - 价钱问题

筛查方法	内容	费用	筛查率	漏诊率	假阳性率	限制性	出报告时间
A 早孕期筛查	超声NT+母血生化指标	500元	90%	10%	5-7%	11至13+6周进行	10个工作日
B中孕期筛查	母血生化指标	200元	65%	35%	5-7%	14至20+6周进行	10个工作日
C无创性产前诊断	胎儿游离DNA	3410元	>99%	<1%	<1%	12周以后	15个工作日
D 侵入性产前诊断	胎儿染色体核型	2400元，包括术前检查	100%，诊断金标准	0	0	有创性，流产率0.5%，11至13+6周开始进行	15个工作日

Thank you

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