



<b>Title</b>	<b>Rapid aneuploidy testing (knowing less) versus traditional karyotyping (knowing more) for advanced maternal age: What would be missed, who should decide?</b>
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<b>Citation</b>	<b>Hong Kong Medical Journal, 2008, v. 14 n. 1, p. 6-13</b>
<b>Issued Date</b>	<b>2008</b>
<b>URL</b>	<b><a href="http://hdl.handle.net/10722/57403">http://hdl.handle.net/10722/57403</a></b>
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# Rapid aneuploidy testing (knowing less) versus traditional karyotyping (knowing more) for advanced maternal age: what would be missed, who should decide?

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## Key words

Abortion, induced; Amniocentesis;  
Aneuploidy; Karyotyping; Prenatal  
diagnosis

*Hong Kong Med J* 2008;14:6-13

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**Objectives** The application of rapid aneuploidy testing as a stand-alone approach in prenatal diagnosis is much debated. The major criticism of this targeted approach is that it will not detect other chromosomal abnormalities that will be picked up by traditional karyotyping. This study aimed to study the nature of such chromosomal abnormalities and whether parents would choose to terminate affected pregnancies.

**Design** Retrospective study on a cytogenetic database.

**Setting** Eight public hospitals in Hong Kong.

**Participants** The karyotype results of 19 517 amniotic fluid cultures performed for advanced maternal age ( $\geq 35$  years) from 1997 to 2002 were classified according to whether they were detectable by rapid aneuploidy testing. The outcomes of pregnancies with abnormal karyotypes were reviewed from patient records.

**Results** In all, 333 (1.7%) amniotic fluid cultures yielded abnormal karyotypes; 175 (52.6%) of these were detected by rapid aneuploidy testing, and included trisomy 21 ( $n=94$ , 28.2%), trisomy 18 or 13 ( $n=21$ , 6.3%), and sex chromosome abnormalities ( $n=60$ , 18.0%). The other 158 (47.4%) chromosomal abnormalities were not detectable by rapid aneuploidy testing, of which 63 (18.9%) were regarded to be of potential clinical significance and 95 (28.5%) of no clinical significance. Pregnancy outcomes in 327/333 (98.2%) of these pregnancies were retrieved. In total, 143 (42.9%) of these pregnancies were terminated: 93/94 (98.9%) for trisomy 21, 20/21 (95.2%) for trisomy 18 or 13, 19/60 (31.7%) for sex chromosome abnormalities, and 11/63 (17.5%) for other chromosomal abnormalities with potential clinical significance. There were no terminations in the 95 pregnancies in which karyotyping results were regarded to be of no clinical significance.

**Conclusions** 'Knowing less' by the rapid aneuploidy stand-alone testing could miss about half of all chromosomal abnormalities detectable by amniocentesis performed for advanced maternal age. Findings from two fifths of the latter were of potential clinical significance, and the parents chose to terminate one out of six of the corresponding pregnancies. If both techniques are available, parents could have enhanced autonomy to choose.

## Introduction

The most frequent foetal chromosomal abnormalities involve the autosomes 21, 18, 13, and sex chromosomes X and Y. Aneuploidy or alterations in copy number of these chromosomes, including trisomy 21 (Down syndrome), trisomy 18 (Edwards' syndrome), trisomy 13 (Patau's syndrome), 45,X (Turner's syndrome), and 47,XXY (Klinefelter's syndrome) account for 80% of clinically significant chromosomal abnormalities diagnosed in the prenatal period. Down syndrome is a well-recognised cause of mental retardation, cardiac, and other congenital abnormalities. Edwards' syndrome and Patau's syndrome lead to multiple congenital abnormalities and early neonatal death. The phenotype of Turner's

syndrome is highly variable and includes short stature, amenorrhoea, infertility, cardiac and renal malformations. Klinefelter's syndrome is associated with a relatively mild phenotype abnormality.

The traditional method for prenatal diagnosis of these common aneuploidies involves analysis of banded metaphase chromosomes from cultured amniotic fluid cells (amniocentesis) or chorionic villi (chorionic villus sampling). It is known as karyotyping, for which all 23 pairs of chromosomes are examined. Apart from the common aneuploidies, a wide range of chromosomal abnormalities can thus be identified by this technique, including rearrangements, such as translocations and inversions that may be balanced or unbalanced. Traditional karyotyping is labour-intensive and the results are usually not available for 2 weeks or more. Advances in molecular diagnostics, using either fluorescence in situ hybridisation (FISH<sup>1-5</sup>) with chromosome-specific DNA probes or quantitative fluorescence-polymerase chain reaction (QF-PCR<sup>6-11</sup>) with chromosome-specific small tandem repeat markers, can be applied to diagnose the common aneuploidies within 1 to 2 days. The sensitivity and specificity of FISH and QF-PCR, collectively described as rapid aneuploidy testing (RAT), have been demonstrated in the aforementioned studies and compare favourably with traditional karyotyping for the diagnosis of the common aneuploidies. Unlike karyotyping, these technologies only allow the identification of the chromosomal abnormalities that are specifically sought (targeted testing).

Currently, RAT (FISH or QF-PCR) is being used to give a rapid result for the common aneuploidies as an adjunct to karyotyping. This combined approach clearly increases the cost of prenatal diagnosis. It has been suggested that if the indication for prenatal diagnosis is an increased risk of Down syndrome arising from a positive screening test result or advanced maternal age, then karyotyping could be replaced by RAT.<sup>9,12-17</sup> This new approach has been challenged, because certain chromosomal abnormalities, although infrequent and usually of debatable significance, would be missed,<sup>5,18-20</sup> which has resulted in much debate in this area of prenatal diagnosis. For example, initiatives by the UK Government<sup>21</sup> to replace traditional karyotyping with new screening programmes involving RAT, FISH, and QF-PCR, were objected by the UK Association of Clinical Cytogeneticists (ACC). Caine et al<sup>22</sup> from the ACC undertook a retrospective cytogenetic audit on 119 528 amniotic fluid and 23 077 chorionic villus samples from 1999 to 2004 to assess the probable clinical impact of these proposed policy changes. They showed that about 1% of all prenatal samples would have a chromosomal abnormality undetected by RAT and that a third of these might have a significant risk of serious phenotypic consequences if RAT was used

## 用於高齡孕婦的快速非整倍體測試與傳統染色體核型分析：缺失與決定權

- 目的** 應用快速非整倍體測試來作為獨立的產前診斷方法備受爭議，其中一個主要的批評是這種方法會遺漏傳統染色體核型分析檢測到的異常染色體。本研究旨在探討這類染色體異常的本質，以及父母會否終止妊娠。
- 設計** 利用細胞遺傳學數據庫進行回顧研究。
- 安排** 香港的八間公營醫院。
- 參與者** 將1997至2002年間為35歲或以上的高齡孕婦19 517個羊水培養基所做的傳統染色體核型分析結果，按可否利用快速非整倍體測試來偵測來分類。此外，亦檢討病歷紀錄中有異常核型的妊娠結果。
- 結果** 共有333例(1.7%)羊水培養基發現異常核型，快速非整倍體測試只能檢測到其中175(52.6%)例，包括了21—三體綜合徵(94例，28.2%)、18—三體綜合徵或13—三體綜合徵(21例，6.3%)、性別染色體異常(60例，18.0%)。其餘158個(47.4%)染色體異常則無法查出，當中63例(18.9%)可能具有臨床意義，95例(28.5%)則無臨床意義。在333例中共檢索到327個(98.2%)妊娠結果紀錄，當中共有143例(42.9%)終止妊娠，所佔比例分別為：94例21—三體綜合徵中有93例(98.9%)終止妊娠，21例18—三體綜合徵或13—三體綜合徵中有20例(95.2%)，60例性別染色體異常中有19例(31.7%)，63例其他染色體異常且可能具臨床意義的有11例(17.5%)。95個傳統染色體核型分析結果顯示不具臨床意義的無一終止妊娠。
- 結論** 快速非整倍體測試所能檢測的染色體異常情況比較少，所以獨立用來為高齡孕婦作產前診斷時，會比起羊水診斷所能測到的染色體異常情況要測漏一半。羊水診斷發現異常的結果中有五分之二具臨床意義，當中每六例中就有一例的父母選擇終止妊娠。假如同時應用兩種檢測，父母的自主權便可加強。

alone.<sup>22</sup> However, these workers had not addressed two important issues relevant to the debate on RAT versus traditional karyotyping.<sup>23</sup> The first was the role of ultrasound examination for structural abnormalities in the foetus. A recent prospective study on 1589 amniocenteses samples obtained for various indications showed that 69% (9/13) of clinically significant chromosomal abnormalities not detectable by RAT had foetal abnormalities detected by ultrasound.<sup>24</sup> Kagan et al<sup>25</sup> had recently shown that more than 98% of all chromosomal abnormalities can be detected if QF-PCR was performed in all samples and karyotyping in about 16% of the samples selected on the basis of ultrasound findings before amniocentesis. The second issue is the clinical outcome of chromosomal abnormalities that are not detectable by the RAT stand-alone approach.<sup>23</sup> The clinical significance of the latter, particularly those without ultrasound-detected foetal abnormalities,

is very different from that of trisomy 21, 18, or 13.<sup>26</sup> Prenatal identification of this group of chromosomal abnormalities often poses difficult counselling issues, as termination of pregnancy (TOP) may be unnecessary and not in the best interests of the parents or the foetus. Here we try to identify the nature of the chromosomal abnormalities from a cohort of pregnancies with amniocenteses performed for advanced maternal age and whether the parents would choose TOP.

## Methods

This study utilised the database of the Prenatal Diagnostic Laboratory, at Tsan Yuk Hospital, which receives all the prenatal samples from eight public hospitals in Hong Kong. The results were sent to the referring hospitals for further action. If necessary, the parents were counselled on the chromosomal abnormalities, mainly by obstetricians in the individual hospital, and in some cases with the help of paediatricians and geneticists. In this database, the indications for amniocentesis were categorised in a hierarchical fashion as follows: (1) ultrasound-detected foetal abnormalities, (2) positive Down syndrome screening, (3) advanced maternal age ( $\geq 35$  years old), and (4) other indications. If one or more ultrasound-detected foetal abnormalities were reported, the case was classified as having ultrasound-detected abnormalities (1); this was irrespective of the Down syndrome screening result or maternal age. If amniocentesis was performed for positive Down screening in a woman aged 35 years or above, the case was classified as (2). We retrospectively reviewed the results of 19 517 amniotic fluid cultures performed specifically for advanced maternal age (3) from 1997 to 2002. Within the same period, there were 1061 amniotic fluid cultures performed for ultrasound-detected foetal abnormalities, 1629 for Down syndrome screening and 2039 cultures for other indications.

The results were categorised into normal and abnormal karyotypes. Abnormal karyotypes were divided into common aneuploidies of chromosomes 21, 18, 13, X and Y, and other chromosomal abnormalities. The latter were further subdivided into a group with potential clinical significance (de-novo balanced translocations and chromosomal rearrangements, unbalanced translocations and chromosomal rearrangements, uncommon autosomal trisomies, de-novo markers) and another group with no clinical significance (balanced translocations/chromosomal rearrangements/markers of familial origin, de-novo balanced Robertsonian translocations). A second classification was performed on whether the results were detectable by RAT. The outcomes of these pregnancies with abnormal karyotypes were reviewed from patient records in each hospital,

through our Working Group on Prenatal Diagnosis and Counselling.

## Results

The results of karyotyping of 19 517 amniotic fluid cultures performed for advanced maternal age from 1997 to 2002 are shown in the Figure. There were 333 (1.7%) abnormal karyotypes. Among these, 175 (53%) were common aneuploidies detectable by RAT. The other 158 (47%) were not detectable by RAT. The latter were further subdivided into 63 (19%) with potential clinical significance and 95 (29%) with no clinical significance.

We obtained the pregnancy outcomes in 327/333 (98.2%) of these patients (Tables 1-3). In total, 143 (43%) pregnancies were terminated; 93/94 (99%) trisomy 21, 20/21 (95%) trisomy 18 or 13, 19/60 (32%) sex chromosome abnormalities, 11/63 (18%) other chromosomal abnormalities with potential clinical significance, and 0/95 (0%) with no clinical significance.

Terminations of pregnancy were separated into two groups. In group 1, they were performed due to major chromosomal abnormalities or major ultrasound-detected structural foetal abnormalities. Major chromosomal abnormalities referred to trisomy 21, 18 and 13 (Table 1), and one case of 5p- or cri-du-chat syndrome (Table 2). Four others of potential clinical significance were terminated because of structural foetal abnormalities detected subsequently by ultrasound examination. They included cleft lip and palate, micrognathia, clinodactyly, microcephaly, aortic stenosis (Table 2). In group 2, although the chromosomal abnormalities were not major and no ultrasound-detected foetal abnormalities were present, the parents could not accept the uncertainty in clinical outcome, which varied from normal to a degree of mental impairment and/or physical abnormality that might not even be evident at birth. Certain sex chromosome abnormalities were also considered under this category.

Table 4 shows the details of the 143 cases with chromosomal abnormalities among those undergoing TOP, of which 25 (18%) belonged to group 2.

## Discussion

The clinical application of RAT as a stand-alone approach in prenatal diagnosis is subject to much debate. The pros and cons of this approach have been discussed in recent review articles.<sup>17,27-31</sup> The major criticism is that such targeted testing would miss the diagnosis of certain chromosomal abnormalities that will be picked up by traditional karyotyping. The counter argument is that 60% of these abnormalities are not clinically significant, and the other 40% are

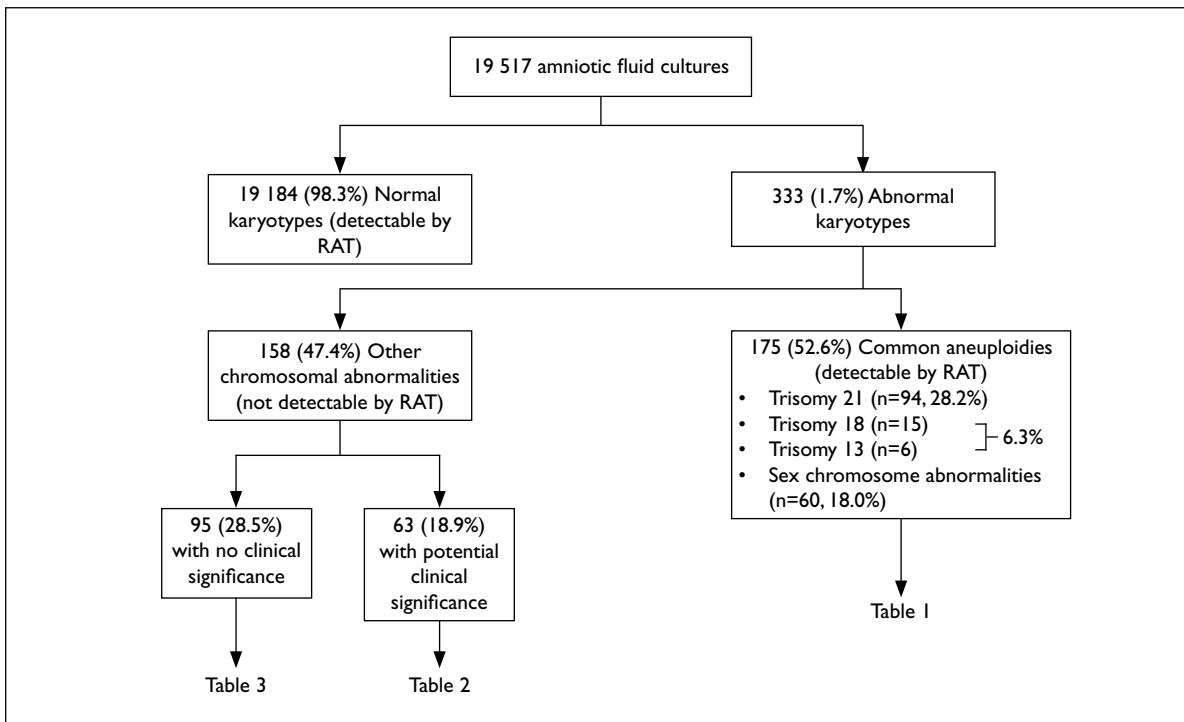


FIG. Traditional karyotyping results of amniocenteses performed for advanced maternal age from 1997 to 2002

RAT denotes rapid aneuploidy testing

TABLE I. Pregnancy outcomes of common aneuploidies detectable by rapid aneuploidy testing (RAT)\*

Chromosomal abnormality	TOP†	TOP‡	Livebirth with no abnormality	Unknown outcome	Total
Trisomy 21	93		1 (mosaic)		94
Trisomy 18	15				15
Trisomy 13	5		1 (mosaic)		6
Sex chromosome abnormalities		19	40	1	60
Mosaic Turner's syndrome		5	11		16
Sex chromosome polysomies (mosaic)		12 (1)	29 (5)	1	42 (6)
Structural X chromosome abnormalities		2			2
<b>Total</b>	<b>113</b>	<b>19</b>	<b>42</b>	<b>1</b>	<b>175</b>

\* TOP denotes termination of pregnancy; the detection of mosaic aneuploidies by RAT depends on the % of mosaicism present; the detection of structural X chromosome abnormalities by RAT depends on the nature of probes (fluorescence in situ hybridisation) or markers (quantitative fluorescence-polymerase chain reaction) used

† TOP for major chromosomal abnormalities

‡ TOP in the absence of major chromosomal abnormalities or major ultrasound-detected structural foetal abnormalities

only of potential clinical significance (excluding those with major ultrasound-detected structural abnormalities in the foetus).<sup>23</sup>

The feasibility of the RAT stand-alone approach depends on the indication for the invasive prenatal test. With the presence of major ultrasound-detected foetal abnormalities, traditional karyotyping should be performed to look for structural chromosomal abnormalities apart from aneuploidies.<sup>13,24,32</sup> The RAT stand-alone approach is best when the invasive prenatal test is performed for an identified increased risk of Down syndrome from a positive Down screening test. We have previously demonstrated

the feasibility of this approach in 1526 cases, with amniocenteses performed for positive biochemical Down screening.<sup>15</sup> For the present study, we chose the much larger dataset of amniocenteses (19 517 cases) performed specifically for advanced maternal age, focusing on the pregnancy outcomes of the 333 cases with chromosomal abnormalities.

As expected, the great majority (98.3%) of amniocenteses performed for advanced maternal age showed normal results (Fig 1). For this large group of parents, RAT could exclude the possibility of foetal Down syndrome and relieve anxiety within 1 to 2 days of amniocentesis.<sup>33</sup> To supplement this



TABLE 2. Pregnancy outcomes of chromosomal abnormalities with potential clinical significance not detectable by rapid aneuploidy testing\*

Chromosomal abnormality	TOP	TOP <sup>§</sup>	Livebirth with no abnormality	Other outcome	Unknown outcome	Total
Balanced translocations (de novo)		1	19	1 miscarriage	1	22
Balanced chromosomal rearrangements (de novo)			17			17
Unbalanced translocations	1 <sup>†</sup>					1
Unbalanced chromosomal rearrangements	1 <sup>†</sup>	4	1	1 miscarriage		7
Other autosomal trisomies	2 <sup>‡</sup> (mosaic)		3 (mosaic)		1	6
Markers (de novo)	1 <sup>†</sup>	1 (mosaic)	6	1 livebirth with abnormality	1	10
<b>Total</b>	<b>5</b>	<b>6</b>	<b>46</b>	<b>3</b>	<b>3</b>	<b>63</b>

\* TOP denotes termination of pregnancy

† TOP for major chromosomal abnormalities

‡ TOP for major ultrasound-detected structural foetal abnormalities

§ TOP in the absence of major chromosomal abnormalities or major ultrasound-detected structural foetal abnormalities

TABLE 3. Pregnancy outcomes of chromosomal abnormalities with no clinical significance not detectable by rapid aneuploidy testing\*

Chromosomal abnormality	TOP	Livebirth with no abnormality	Other outcome	Unknown outcome	Total
Balanced translocations, chromosomal rearrangements, markers of familial origin		86	1 livebirth with abnormality 1 intra-uterine death	2	90
Balanced Robertsonian translocations (de novo)		5			5
<b>Total</b>		<b>91</b>	<b>2</b>	<b>2</b>	<b>95</b>

\* TOP denotes termination of pregnancy

fast report with the traditional karyotyping (whose results become available) in 2 to 3 weeks seems unnecessary.

The pregnancy outcomes of the various common aneuploidies detectable by RAT could be very different (Table 1). Essentially, all cases with non-mosaic trisomies 21, 18 and 13 were terminated. If RAT was performed, the decision to terminate the pregnancies could be made 2 to 3 weeks earlier.<sup>34</sup> On the other hand, sex chromosome abnormalities pertained to another issue (Table 1). None of them had major ultrasound-detected foetal abnormalities in this dataset of amniocenteses performed for advanced maternal age. Two thirds of the parents decided to continue with the pregnancies, which resulted in livebirths with no morphological abnormality at birth, while the other third decided to terminate the pregnancies. Not surprisingly the prognosis of persons with sex chromosome abnormalities is very different from that of trisomies 21, 18 and 13. Thus, some obstetricians, clinical geneticists, and genetic counsellors are uneasy about testing and reporting the sex chromosome status of all foetuses undergoing invasive prenatal tests.<sup>35-37</sup> Identification of sex chromosome abnormalities such as XXX, XYY and XXY (Klinefelter's syndrome), that are either asymptomatic or associated with a relatively mild phenotype, often poses difficult counselling issues and may not be in the best interests of the parents.

Such findings tend to increase parental anxiety and present a difficult choice regarding the continuation of the pregnancy. On the other hand, the Turner's syndrome (45,X) phenotype is highly variable with respect to short stature, amenorrhoea, infertility, cardiac malformations (coarctation of aorta) and renal complications.<sup>38</sup> Besides, up to 99% of foetuses with Turner's syndrome are miscarried during the first and second trimester of pregnancy,<sup>39</sup> and those that do not miscarry usually have ultrasound abnormalities.<sup>40</sup> Donaghue et al<sup>37</sup> has proposed a selective policy for foetal sexing if RAT is to be used as a stand-alone test. Aneuploidies of X and Y chromosomes will be determined by RAT only in cases displaying ultrasound abnormalities consistent with Turner's syndrome and those at risk of inheriting a sex-linked disorder. The ultrasound findings in Turner's syndrome include: cystic hygroma, nuchal thickening of 5 mm or more, adjusted nuchal risk of 1:5 or higher, hydrops, nuchal oedema or coarctation of the aorta.<sup>37</sup> This targeting policy for sex chromosome tests may avoid the unintentional finding of conditions of borderline significance, such as XXX, XYY and XXY, during prenatal testing for Down syndrome.

When amniocenteses were performed for advanced maternal age, chromosomal abnormalities not detectable by RAT (Tables 2 and 3) were unexpected by the couples as well as the obstetricians.<sup>41</sup> They would have been excluded from prenatal testing, if RAT

TABLE 4. Chromosomal abnormalities with termination of pregnancy (TOP)

Chromosomal abnormality	No. with TOP	Details of chromosomal abnormalities with TOP	No.
Common autosomal aneuploidies	113/115 (98.3%)	Trisomy 21	93
		Trisomy 18	15
		Trisomy 13	5
Mosaic Turner's syndrome	5/16 (31.3%)	45,X[7]/46,XX [40]	1*
		45,X[16]/46,XX [14]	1*
		45,X[2]/47,XXX[6]/46,XX [45]	1*
		45,X[5]/47,XXX[15]/46,XX [40]	1*
		45,X,inv(9)(p11q13)[13]/46,X,i(X)(q10),inv(9)(p11q13) [47]	1*
Sex chromosome polysomies	12/42 (28.6%)	47,XXY	9*
		47,XYY[19]/46,XY [31]	1*
		47,XXX	2*
Structural X chromosome abnormalities	2/2 (100%)	46,X,Xp-	1*
		46,X,i(X)(q10)	1*
Balanced translocations (de novo)	1/22 (4.5%)	46,XX,t(2;13)(q32;q21)de novo	1*
Unbalanced translocations	1/1 (100%)	46,XX,der(10)t(10;22)(q26.1;q11.2)pat	1
Unbalanced chromosomal rearrangements	5/7 (71.4%)	46,XX,2p+ de novo	1*
		46,XY,11q-,13q- de novo	1*
		46,XY,5p- de novo	1
		46,XY,5p+ de novo	1*
		46,XY,9p+ de novo	1*
Other autosomal trisomies	2/6 (33.3%)	47,XX,+20[14]/46,XX [26]	1
		47,XX,+9[47]/46,XX [53]	1
Markers (de novo)	2/10 (20.0%)	47,XY,+mar de novo	1
		47,XY,+mar[14]/46,XY [47]	1*
<b>Total</b>			<b>143 (25*)</b>

\* TOP in the absence of major chromosomal abnormalities or major ultrasound-detected structural foetal abnormalities

were applied as a stand-alone test in the absence of ultrasound-detected structural foetal abnormalities. Some of them had potential clinical significance (Table 2) while others had no clinical significance (Table 3). For those chromosomal abnormalities with potential clinical significance (Table 2), 49 couples decided to continue with the pregnancies. Eleven couples decided to terminate the pregnancies: four owing to the presence of foetal abnormalities (cleft lip and palate, micrognathia, clinodactyly, microcephaly, aortic stenosis), which were discovered during subsequent ultrasound examinations after the chromosomal abnormalities were identified (ie group 1, Table 2). One termination was for 5p- (cri-du-chat) syndrome and the other six because the parents could not accept the uncertainty in clinical outcome varying from normal to a certain degree of mental impairment and physical abnormalities, which might not be diagnosed even at birth (ie group 2, Table 2).<sup>42</sup> So, what might ensue if RAT is replaced by traditional karyotyping? The 5p- syndrome would be missed. The other six chromosomal abnormalities with potential clinical significance would not be

diagnosed and the respective parents would not have the chance to consider TOP.

For chromosomal abnormalities with no clinical significance (Table 3), karyotyping provided no useful additional information (except that the finding of a familial translocation will have implications for future pregnancies). Instead it led to additional counselling time to convey information and to relieve parental anxiety. None of these 95 cases had TOP.

Overall, 143 pregnancies were terminated, 25 (17.5%) of them belonged to the group in which the chromosomal abnormalities were not major (19 sex chromosome abnormalities and six chromosomal abnormalities with potential clinical significance) and there were no major ultrasound-detected structural foetal abnormalities (Table 4). If RAT (for trisomies 21, 18 and 13 only) had been used as a stand-alone approach, it could have been coupled with RAT testing for sex chromosome aneuploidies only when ultrasound-detected abnormalities were consistent with Turner's syndrome.<sup>37</sup> In which case, traditional karyotyping would only be needed when there

were major ultrasound-detected structural foetal abnormalities,<sup>13,24,32</sup> and consequently the 25 cases without major abnormalities would not be diagnosed and the parents would not have the option to terminate these pregnancies. One might argue that this is a beneficence-based approach (the physician making decisions that are best for the patient, without regard to personal gain or the interests of others). Some of these 25 TOP were probably unnecessary because the chromosomal abnormalities are only of potential clinical significance, particularly in the absence of ultrasound-detected foetal abnormalities. On the other hand, the ethics of prenatal diagnosis should be autonomy-based (the capacity of a rational individual to make an informed, uncoerced decision; in medicine, respect for the autonomy of patients is considered obligatory for doctors and other health care professionals). If the parents choose to have TOP for minor chromosomal abnormalities, we have the obligation to make sure that the counselling is thorough, to ensure that they have the information about the outcomes in order to exercise their autonomy to continue or terminate the pregnancy. If after that process, the parents still choose to

terminate the pregnancy, then their decision and autonomy must be respected. A medical attitude of "we will not look for sex chromosome abnormalities and other minor chromosomal abnormalities as we do not consider you should have a termination" could be considered paternalistic (a figurehead that makes decisions on behalf of others for their own good, even if this is contrary to their wishes). If both techniques are available, parents should have the autonomy to choose the approach (RAT, or traditional karyotyping, or both) after being fully informed of the pros and cons. Bui<sup>43</sup> recently reported their experience in Stockholm, when Swedish women were given this choice, 70% of them chose the RAT stand-alone approach.<sup>43</sup> It would be interesting to study the parental preference in our Chinese population, particularly in Mainland China, which operates a one-child policy.

## Acknowledgement

We would like to thank Prof Frank Chervenak, Weill Medical College of Cornell University, New York, for his comments on the manuscript.

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