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Chromosomal abnormalities and *FMR1* gene premutation in Chinese women with premature menopause

更年期過早的華裔女性的染色體異常和*FMR1*基因先期突變

Objective. To study the prevalence of chromosomal abnormalities and *FMR1* gene premutation in Chinese women with premature menopause in Hong Kong.

Design. Retrospective study.

Setting. Clinical Genetic Service, Hong Kong.

Participants. Chinese women with premature menopause referred for cytogenetic study from January 1983 to November 2003.

Main outcome measures. Chromosomal abnormalities, *FMR1* gene premutation.

Results. Chromosomal abnormalities were present in 15.6% of Chinese women who suffered premature menopause. X-chromosome abnormality was involved in over 80% of cases. *FMR1* gene premutation was present in 0.86% of 116 cases screened for this abnormality. The predominance of X-chromosome abnormality accounted for the shorter stature, younger menopausal age, and higher prevalence of dysmorphic features among the cytogenetically abnormal patients. However, on logistic regression, no clinical feature was significantly correlated with cytogenetic abnormality.

Conclusions. The prevalence of chromosomal abnormalities among Hong Kong Chinese women who suffer premature menopause was comparable with that of Caucasian and Chinese populations elsewhere. Because clinical features are poor predictors of cytogenetic abnormality, a pragmatic approach to screening is advocated. The carrier rate of fragile X premutation in these women appeared lower than that of Caucasians. Nevertheless, a search for *FMR1* gene premutation, in addition to conventional chromosomal study, has important implication for prenatal diagnosis and fertility management for the extended family.

目的：研究更年期過早的香港華裔女性出現染色體異常和*FMR1*基因先期突變的情況。

設計：回顧研究。

安排：衛生署醫學遺傳科，香港。

參與者：1983年1月至2003年11月期間，因更年期過早獲轉介接受細胞遺傳學檢查的華裔女性。

主要結果測量：染色體異常和 *FMR1* 基因先期突變。

結果：在患有更年期過早的華裔女性當中，15.6%出現染色體異常，當中超過80%患有X染色體異常。在116宗病例當中，0.86%出現*FMR1*基因先期突變。在細胞遺傳異常的病人中，X染色體異常是造成身型矮小、更年期較早，以及畸形情況較為普遍的主因。不過，對數迴歸分析則顯示，沒有任何臨床症狀是和細胞遺傳異常顯著相關。

結論：在更年期過早的香港華裔女性病人中，染色體異常的普遍程度與白

Key words:
Fragile X syndrome;
Menopause, premature;
Ovarian failure, premature;
X chromosome

關鍵詞：
脆性X染色體綜合徵；
更年期，過早；
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人及其他地方的華裔女性相若。由於臨床症狀並不能有效預測細胞遺傳異常，病人應接受篩查。雖然香港華裔女性脆性X染色體先期突變的帶因率比白人為低，不過，傳統的染色體研究，加上 *FMR1* 基因先期突變測試，對病人下一代的產前診斷和生育管理都是非常重要的。

Introduction

Premature menopause affects 1% to 3% of the female population and refers to cessation of ovarian activity before 40 years of age.[1] Although it has long been recognised that certain cases are associated with chromosomal and genetic disorders, local data have not been reported.

This local study represents the largest epidemiological study ever conducted for cytogenetics of premature menopause. It is the first time that cytogenetics for Chinese women suffering premature menopause have been reported in the English literature. It is also the first report of screening for *FMR1* gene premutation in the Chinese population.

Methods

This retrospective study was carried out, following ethical approval, at the Clinical Genetic Service, Department of Health, Hong Kong. An initial computer search on 'secondary amenorrhoea and premature menopause' was made on the clinical information system and patient records retrieved for the period 1 January 1983 to 30 November 2003.

Patients were included in the study if they were Chinese, had secondary amenorrhoea for at least 1 year with an onset of less than 40 years, and had menopausal state confirmed by one of the following: confirmed diagnosis by referring gynaecologist, menopausal symptoms, or elevated follicle-stimulating hormone (FSH) level. Follicle-stimulating hormone level was regarded as elevated if it was higher than 20 IU/L or described as 'elevated' or 'in the postmenopausal range' by the referring gynaecologist.

In all patients, cultured peripheral blood lymphocytes were karyotyped using standard G-banding technique. Routine *FMR1* gene testing was also offered to patients referred after 2000. DNA was extracted from peripheral blood. High-resolution polymerase chain reaction followed by GeneScan analysis was employed. Women with two normal-sized alleles were considered normal. Those with only one normal-sized allele were subject to Southern blotting analysis to differentiate between normal homozygote and true premutation.

Table 1. Diagnosis of premature menopause

Diagnostic feature in addition to amenorrhoea (>1 year)	Cases, n=295 No. (%)
FSH* level >20 IU/L	142 (48.1)
FSH level not available	
'Elevated FSH' or 'FSH in menopausal range' on gynaecologist's referral letter	80 (27.1)
'Premature ovarian failure' or 'premature menopause' on gynaecologist's referral letter	72 (24.4)
Vasomotor symptoms	1 (0.4)

* FSH follicle-stimulating hormone

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], United States). Systematic cross-checking of computer spreadsheet data with original case records was made to ensure accuracy of data entry. The statistical significance level was set at 0.05 by two-tailed analysis.

Results

A total of 370 cases of 'secondary amenorrhoea and premature menopause' between 1 January 1983 and 30 November 2003 were identified on the clinical information system. All case notes were successfully retrieved through the record office. A total of 295 cases fulfilled the inclusion criteria: all had a karyotyping on G-banding and 116 (39.3%) additionally had molecular test of the *FMR1* gene.

Diagnosis of premature menopause

All patients reported secondary amenorrhoea of 1 year's duration with an onset before 40 years of age. Their menopausal state was additionally confirmed as shown in Table 1.

Chromosomal abnormalities

A total of 46 (15.6%) women had an abnormal cytogenetic study (Table 2). More than 80% of abnormalities involved at least some part of the X chromosome, almost half due to monosomy X and its variants. In addition, autosomes were not entirely silent in terms of ovarian function: they were the only chromosome at fault in 13.0% of cases.

Over the past 20 years, the number of referrals to

Table 2. Distribution of cytogenetic abnormalities

Category	Cytogenetic abnormality	No. of cases	Subtotal, n=46 No. (%)
Monosomy X and its variants	Pure monosomy X (45,X)	5	22 (47.8)
	Mosaic monosomy X and X-chromosome structural abnormalities	3	
	Mosaic monosomy X (45,X/46,XX)	11	
	Mosaic monosomy X and trisomy	3	
X-chromosome structural abnormalities only	Isochromosome Xq	1	9 (19.6)
	Deletions on Xq	8	
X-autosome translocation	X-chromosome 22 translocation	1	2 (4.3)
	X-chromosome 14 translocation	1	
Excessive No. of X chromosomes	Mosaic trisomy X (46,XX/47,XXX)	2	6 (13.0)
	Pure trisomy X (47,XXX)	3	
	Cell lines mosaic for variable copies of X chromosomes 46,XX (96%)/48,XXXX (2%)/49,XXXXX (2%)	1	
Y chromosome	Mosaic cell lines one of which contains Y chromosome 45,X (10%)/46,XX (20%)/46,XY (70%)	1	1 (2.2)
Autosome*	Chromosome 18 deletion	1	6 (13.0)
	Mosaic marker chromosome of undetermined origin	1	
	Chromosome 22 deletion	1	
	Extra length on q arm of chromosome 1	1	
	Balanced translocation between chromosome 1 and 8	1	
	Extra heterochromatin on q arm of chromosome 9	1	

* Two cases with 46,XX,inv(9)(p11q13) were excluded because they are known normal variant

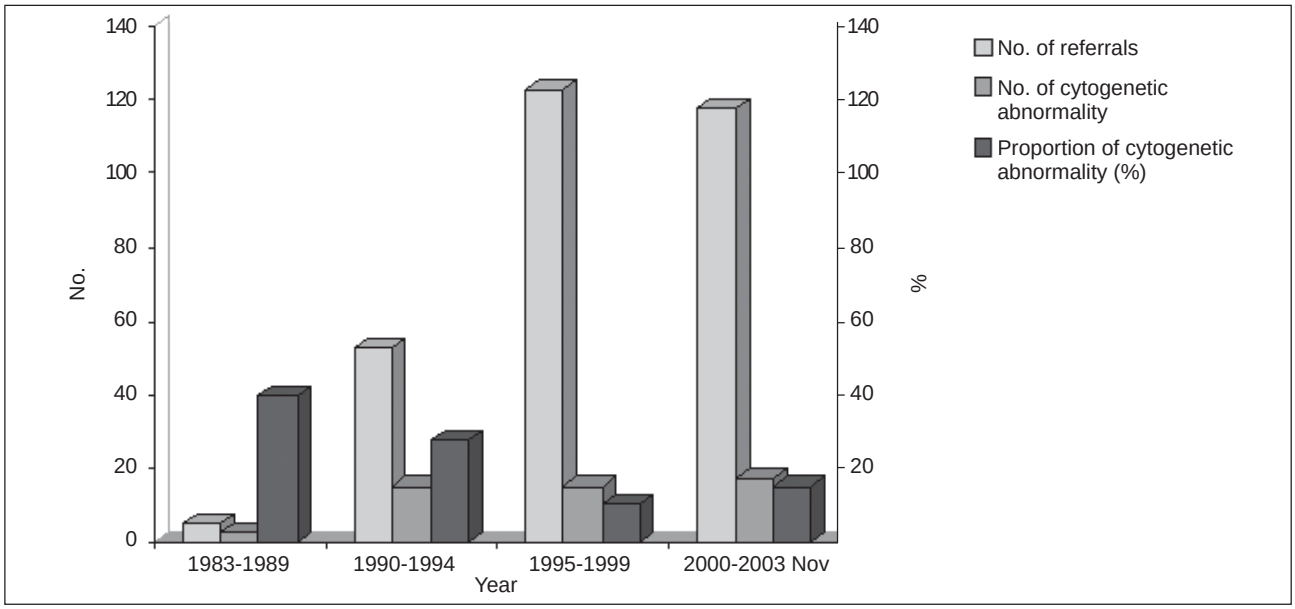

Fig 1. Case referrals for cytogenetic study over the past 20 years

the genetic service for premature menopause has increased (Fig 1). Although the detection rate of cytogenetic abnormalities decreased initially, it is now stable at 10% to 15%.

Correlation with clinical features

Cytogenetically normal versus abnormal

The mean age at menopause for those with chromosomal abnormalities was 28.2 years, significantly younger than those without (mean, 31.0 years; P<0.01). Those with an abnormality were also shorter in stature (mean, 151.1 cm vs 157.1 cm; P<0.01). However, there was no statistically significant difference between the two groups in terms of mean FSH level at presentation and family history of mental retardation or premature menopause.

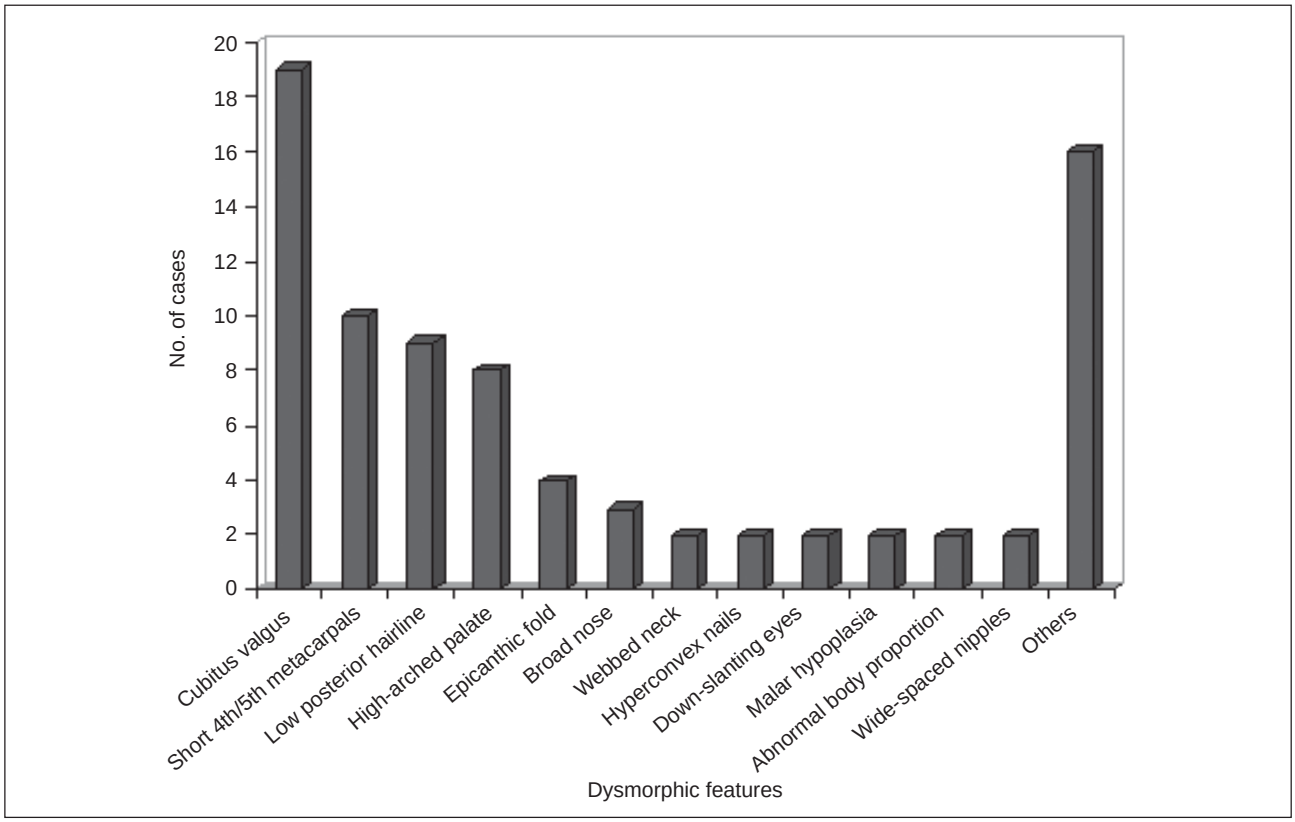

Fig 2. Profile of dysmorphic features

Dysmorphic features were identified in 16% of the referred women prior to cytogenetic study (Fig 2). The prevalence significantly increased to 34% for the group with confirmed cytogenetic abnormality, compared with 13% among those with a negative cytogenetic study ($P<0.05$). Of all the referrals, 5.4% had more than one dysmorphic feature, and 3% more than two. Likelihood of cytogenetic abnormality increased linearly with the number of dysmorphic features (linear-by-linear association, 12.5; $P<0.01$). For those with three or more dysmorphic features, 50% had cytogenetic abnormalities. Nonetheless, analysis of individual dysmorphic features revealed that none of them by itself was significantly more prevalent when cytogenetic abnormality was present.

Logistic regression was used to determine whether clinical information collected at the first encounter could predict cytogenetic abnormality. Such information included the age at menopause, body stature, presence of mental retardation, dysmorphic features, and family history of premature menopause or mental retardation. None was significantly associated with cytogenetic abnormality.

Sex chromosome versus pure autosome abnormalities

The clinical features of 40 cases of sex chromosome abnormalities were compared with six cases of pure autosome defects: those with normal cytogenetic study served as controls. Analysis of variance test was employed for data on ratio scale. The mean age at menopause was 28.0, 29.7, and 31.0 years, with mean body height of 150.1 cm, 155.9 cm, and 157.2 cm, and prevalence of dysmorphic features of 37%, 17%, and 13%, respectively for the three groups. Significant differences were detected only between those with sex chromosome abnormalities and the control ($P=0.03$ for age, $P<0.01$ for height, and $P=0.01$ for prevalence of dysmorphic features). The FSH level was similar among the three groups.

These results signified that the younger menopausal age, shorter stature, and the higher prevalence of dysmorphic features among the cytogenetically abnormal patients were solely contributed by the high proportion of sex chromosomal abnormalities within this group.

The X chromosome: numerical versus structural abnormalities

Sixteen patients with monosomy X (45,X or 45,X/46,XX) were compared with nine patients with X-chromosome structural defects and six patients with excessive copies of X chromosomes. Those with nor-

Table 3. Deletions on q arm of X chromosome

Case No.	Point of deletion	Age at menopause (years)	Height (cm)	Dysmorphic feature
C9838	46,X,del(X)(q27.2)	30	151	-
C3060	46,X,del(X)(q26)	28	147	Epicanthic fold
C7624	46,X,del(X)(q24)	29	-	Cubitus valgus
C5290	46,X,del(X)(q23)	18	150	Cubitus valgus, bilateral small and low-set ears, anteverted nostrils
C1570	46,X,del(X)(q22)	13	134	-

mal cytogenetic study served as controls. Analysis of variance test was used for data on ratio scale. There was no difference in the age at menopause or mean FSH level across the four groups.

Patients with monosomy X and X-chromosome structural defects had similar body stature (147.5 cm vs 146.1 cm; P=0.98). Those with excessive copies of X chromosomes were also similar in height to the control group (165.3 cm vs 157.2 cm; P=0.14). When compared with the former two entities, the latter two were nonetheless significantly taller (P<0.01).

The prevalence of dysmorphic features among the four groups was 13% for the controls, 17% for those with excessive copies of X chromosomes, 31% for those with monosomy X, and 56% for those with X-chromosome structural defects. A difference was detected only between the last group and the controls (P<0.01).

Therefore, while X-chromosome structural defects contributed significantly to the higher prevalence of dysmorphic features among sex chromosome abnormalities, structural and numerical X-chromosome defects played a role in determining short stature. Other sex chromosome abnormalities might however account for the younger age at menopause for sex chromosome abnormalities.

Xq deletions: extent of lesion and the clinical effect

Although patient numbers were too small to allow definitive conclusions, it would appear that the extent of lesion on the q arm of X chromosome had affected menopausal age, other clinical effects being less obvious (Table 3).

FMR1 *gene premutation*

Of the 116 cases who presented after 2000, one (0.86%) had fragile X premutation. The number of CGG repeats was 92 (normal: <54, full mutation: >200). She had a positive family history of mental retardation but not of premature menopause. Unfortunately, she defaulted from further follow-up and the family were not available for further testing.

Discussion

To date, a total of nine studies have examined the prevalence of cytogenetic abnormalities among women with premature menopause (Table 4).[2-10] This study is the largest one and the only one in the English literature to report the cytogenetics of premature menopause in Chinese women. Over the past 20 years, the number of referrals has increased. The increased readiness to refer is reflected by a corresponding drop in detection rates of cytogenetic abnormalities. The current abnormal karyotype rate of 15.6% is in line with western data and the Chinese premature menopausal population elsewhere.[2,3]

Consistent with previous study findings, X-chromosome abnormality is the main contributor to cytogenetic abnormality among women undergoing premature menopause. It accounts for many of the clinical features in the cytogenetically abnormal group, including younger age at menopause, shorter stature, and higher prevalence of dysmorphic features. The deficiency of genetic material on the X chromosome, be it numerical (Turner variant) or structural, has a stronger impact on clinical presentation than redundancies (trisomy X and variants). On the contrary, autosomal abnormalities among this population are relatively silent in terms of their effect on clinical features.

Although no clinical feature is significantly associated with the presence of cytogenetic abnormality, patients who are cytogenetically abnormal are more likely to have shorter stature, younger menopausal age, and identifiable dysmorphism. When more than three dysmorphic features are identified, there is a 50% chance of cytogenetic abnormality. The FSH level and family history are not helpful.

Turner variants are the most common sex chromosome abnormality in women with premature menopause and account for almost 50% of the cyto-

Table 4. Earlier studies on the cytogenetics of premature menopause

	Zhang,[2] 2003	Lu,[3] 1995	Lin and Yu,[4] 1996	Castillo et al,[5] 1992	Tanaka et al,[6] 1988	Davison et al,[7] 1998	Devi and Benn,[8] 1999	Board et al,[9] 1979	Rebar and Connolly,[10] 1990*	Present study
Location	Chongqing, China	Shanghai, China	Shanghai, China	Chile	Japan	London, United Kingdom	Farmington, United States	United States	Ohio, United States	Hong Kong
Sample size	104	Not available	41	47	14	62	30	8	45	295
No. of cytogenetic abnormality	13 (12.5%)	- (14.8%)	9 (22.0%)	- (32.0%)	2 (14.3%)	1 (1.6%)	4 (13.3%)	1 (12.5%)	6 (13.3%)	47 (15.9%)
Monosomy X	3	-	3	(25.7%)	1	-	1	1	2	22
X deletion	4	-	1	-	1	1	-	-	-	8
Isochromosome X	-	-	1	-	-	-	1	-	-	1
X inversion	1	-	-	-	-	-	-	-	-	0
Dicentric X	1	-	-	-	-	-	-	-	-	0
Y-fragment	-	-	-	-	-	-	1	-	-	1
X-autosome translocation	1	-	2	1	-	-	1	-	1	2
Fragile X premutation	NT†	NT	NT	NT	NT	NT	NT	NT	NT	1
Trisomy X	1	-	2	2	-	-	-	-	3	6
Autosomal abnormality	-	-	-	-	-	-	-	-	-	6

* Patients were younger than 30 years at menopause
† NT not tested

genetic diagnoses. There are evidences showing that low level of 45,X/46,XX mosaics that can be detected by fluorescent in situ hybridisation (FISH) but missed on routine cytogenetic analysis may account for even more cases of premature menopause.[11,12] Mosaic 45,X/47,XXX are considered Turner variants because they are phenotypically similar to the 45,X/46,XX.[13] The current view is that in monosomy X, the pathogenesis of germ cell failure is increased atresia secondary to meiotic pairing errors, not deficient germ cell formation.[14] Isochromosome Xq also behaves like monosomy X. Duplication of Xq does not compensate for deficient Xp.[13] Patients are universally short because the gene for short stature (*SHOX*) is on Xq.

About 70% of terminal deletions of the X chromosome lead to premature menopause. Both incidence and severity increase proportionally with the increasing loss of DNA from the two far ends of the X chromosome to a maximum at Xq13, more or less at the centre of the chromosome.[15] There are two regions on Xq that are hypothesised to contain putative genes related to premature ovarian failure (POF): the POF1 region at Xq26-28 and a more recently designated region of Xq22 now termed POF2.[16] Because the presentation is variable, it is highly likely that there are other genes on Xq involved in POF. The actual mechanism is much more complicated.

Balanced X-autosome translocations very often lead to POF.[15] Two cases of X-autosome translocation with premature menopause were identified in this study. Another study showed that most X-autosome translocations associated with POF do not interrupt X-linked genes. Instead, they cause premature menopause by a chromosomal effect, such as inhibition of meiotic pairing or altered X inactivation.[17]

The current study is the first to report the results of fragile X premutation screening among Chinese women with premature menopause. This study identified one premutation carrier among 116 consecutive cases screened. The estimate of premutation carriers is 13.8% and 2.1%, respectively for familial and sporadic cases of POF in western populations.[18,19] The reported rate of 0.86% in this study is much lower.

Studies have identified differences between Chi-

nese and Caucasian women in the structure of the CGG repeat on the *FMR1* gene.[20,21] No differences have been found in the repeated pattern in subjects from four Chinese cities (Hong Kong included), suggesting no geographical differences among Chinese populations.[22] Our reported rate of 0.86% may therefore be applicable to Chinese women elsewhere.

The causes of POF in premutation carriers remain unidentified. It has been postulated that factors related to genomic imprinting[23] or the higher incidence of dizygotic twinning in female carriers of premutation may be implicated.[24-27] Alternatively, the mRNA with the large repeat may affect ovarian development or function[28] or interfere with X inactivation.[29]

When a woman is found to be a premutation carrier, the expansion of trinucleotide repeats to full mutation during female meiosis may result in mentally retarded offspring. Prenatal screening should be offered. The extended family should also be screened and women who may have premature menopause identified and appropriately counselled.

Chromosomal defects related to premature menopause have been reported over various autosomes.[16,30,31] It is unclear if they reflect disruption of autosomal loci integral to ovarian preservation and oogenesis. That no chromosome is consistently involved suggests non-specific meiotic perturbation.[32]

In addition to chromosomal abnormalities and *FMR1* gene premutation, many other genetic mechanisms pertain to the aetiology of premature menopause. The cytogenetic diagnosis revealed here may represent just 'the tip of the iceberg'. Other rare entities are nonetheless less definite and many are still the subject of active research.

In the present review, FISH and molecular study were not used to further delineate the break point in those with structural chromosomal abnormality. The use of FISH or molecular study improves the accuracy and precision in diagnosis. However, it is costly and the additional information thus gained is so subtle that it does not influence management. Molecular and FISH studies are therefore not routinely performed.

Conclusion

The prevalence of cytogenetic abnormalities among Hong Kong Chinese women with premature menopause is similar to that seen in Caucasian and Chinese populations elsewhere. Among all cytogenetic abnormalities, monosomy X and its variants predominate. Although cytogenetically abnormal women are shorter in stature, of younger age at menopause, and higher prevalence of dysmorphism, clinical features are generally poor predictors of cytogenetic abnormality. A pragmatic approach to screening is advocated.

The prevalence of *FMR1* gene premutation carrier among Chinese women with premature menopause was around 0.86%. Workup for premature menopause in Chinese women should include testing for *FMR1* premutation. It has practical implications for counselling, prenatal diagnosis, and fertility management.

References

1. Anasti JN. Premature ovarian failure: an update. Fertil Steril 1998;70:1-15.
2. Zhang J. A study of hypergonadotropic secondary amenorrhea with cytogenetics [in Chinese]. Journal of Chongqing Medical University 2003;28:151-2.
3. Lu JZ. Study on cytogenetics of 2269 cases [in Chinese]. Contemporary Progress in Obstetrics and Gynecology 1995;4:235-7.
4. Lin J, Yu C. Hypergonadotropic secondary amenorrhea: clinical analysis of 126 cases [in Chinese]. Zhonghua Fu Chan Ke Za Zhi 1996;31:278-82.
5. Castillo S, Lopez F, Tobella L, Salazar S, Daher V. The cytogenetics of premature ovarian failure [in Spanish]. Rev Chil Obstet Ginecol 1992;57:341-5.
6. Tanaka S, Mizunuma M, Watanabe H, Hata H, Shimoya Y, Hashimoto M. Premature ovarian failure: a clinical, histological and cytogenetic study. Asia Oceania J Obstet Gynaecol 1988;14:293-300.
7. Davison RM, Quilter CR, Webb J, et al. A familial case of X chromosome deletion ascertained by cytogenetic screening of women with premature ovarian failure. Hum Reprod 1998; 13:3039-41.
8. Devi A, Benn PA. X-chromosome abnormalities in women with premature ovarian failure. J Reprod Med 1999;44:321-4.
9. Board JA, Redwine FO, Moncure CW, Frable WJ, Taylor JR. Identification of differing etiologies of clinically diagnosed premature menopause. Am J Obstet Gynecol 1979;134: 936-44.
10. Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. Fertil Steril 1990;53: 804-10.
11. Diao FY, Xu M, Liu JY. Analysis of X chromosome mosaicism in patients with premature ovarian failure by fluorescent in-situ hybridization [in Chinese]. Zhonghua Fu Chan Ke Za Zhi 2003;38:20-3.
12. Devi AS, Metzger DA, Luciano AA, Benn PA. 46,X/46,XX mosaicism in patients with idiopathic premature ovarian failure. Fertil Steril 1998;70:89-93.
13. Simpson JL, Rajkovic A. Ovarian differentiation and gonadal failure. Am J Med Genet 1999;89:186-200.
14. Ogata T, Matsuo N. Turner syndrome and female sex chromosome aberrations: deduction of the principal factors involved in the development of clinical features. Hum Genet 1995;95:607-29.

15. Schlessinger D, Herrera L, Crisponi L, et al. Genes and translocations involved in POF. Am J Med Genet 2002;111: 328-33.
16. Layman LC. Genetic causes of human infertility. Endocrinol Metab Clin North Am 2003;32:549-72.
17. Prueitt RL, Chen H, Barnes RI, Zinn AR. Most X;autosome translocations associated with premature ovarian failure do not interrupt X-linked genes. Cytogenet Genome Res 2002; 97:32-8.
18. Conway GS, Payne NN, Webb J, Murray A, Jacobs PA. Fragile X premutation screening in women with premature ovarian failure. Hum Reprod 1998;13:1184-7.
19. Marozzi A, Vegetti W, Manfredini E, et al. Association between idiopathic premature ovarian failure and fragile X premutation. Hum Reprod 2000;15:197-202.
20. Zhong N, Liu X, Gou S, et al. Distribution of FMR-1 and associated microsatellite alleles in a normal Chinese population. Am J Med Genet 1994;51:417-22.
21. Chen SH, Schoof JM, Buroker NE, Scott CR. The identification of a (CGG)6AGG insertion within the CGG repeat of the FMR1 gene in Asians. Hum Genet 1997;99:793-5.
22. Wu XQ, Jiang ZY, Yin CH, et al. Investigation and analysis of FMR-1 alleles in the normal population [in Chinese]. Shanghai Med J 2000;23:88-90.
23. Hundscheid RD, Sistermans EA, Thomas CM, et al. Imprinting effect in premature ovarian failure confined to paternally inherited fragile X premutations. Am J Hum Genet 2000;66: 413-8.
24. Tizzano EF, Baiget M. High proportion of twins in carriers of fragile X syndrome. J Med Genet 1992;29:599.
25. Turner G, Robinson H, Wake S, Martin N. Dizygous twinning and premature menopause in fragile X syndrome. Lancet 1994; 344:1500.
26. Healey SC, Duffy DL, Martin NG, Turner G. Is fragile X syndrome a risk factor for dizygotic twinning? Am J Med Genet 1997;72:245-6.
27. Martin NG, Healey SC, Pangan TS, Heath AC, Turner G. Do mothers of dizygotic twins have earlier menopause? A role for fragile X? Am J Med Genet 1997;69:114-6.
28. Sherman SL. Premature ovarian failure in the fragile X syndrome. Am J Med Genet 2000;97:189-94.
29. Vialard F, Cocquet J, Christin-Maitre S, Veitia R, Fellous M. The X chromosome and ovarian function. Cytogenet Genome Res 2002;99:218-22.
30. Laml T, Preyer O, Umek W, Hengstschlager M, Hanzal H. Genetic disorders in premature ovarian failure. Hum Reprod Update 2002;8:483-91.
31. Simpson JL. Ovarian maintenance determinants on the X chromosome and on autosomes. In: Coutifaris C, Mastroianni L, editors. New horizons in reproductive medicine. New York: Parthenon; 1997:439-44.
32. Van Assche E, Bonduelle M, Tournaye H, et al. Cytogenetics of infertile men. Hum Reprod 1996;11(Suppl 4): 1S-26S.