2012年1月16日中日新聞コラム「紙つぶて」

紙つぶて

不育症

杉浦　真弓

私の研究テーマは不育症です。不育症とは、妊娠はするけれど流産、死産を繰り返して子が得られない場合をいい、患者さんが多い割に不妊症ほど知られていません。わが国の不育症頻度は4・2%、38%の女性が流産を経験している、という私たちの調査結果を報じた記事が、二〇〇九年八月の中日新聞に掲載されました(掲載時は途中結果)。

女性は流産を隠す傾向にあります。流産は仕事や不摂生のせいで起こるといった偏見のため、自分を責める女性もいます。不育症が認知されることで、孤立していた患者さんの精神的苦痛が、少し和らぐことが期待できます。

流産の80%は胎児の染色体異常によって起こります。例えば妊娠七週がその子の寿命なのです。不育症の方は薬剤が効くのはごく一部で、多くの方は薬物を必要としません。それでも85%が出産に至ります。

別の記事では、高額の医療費を払っている不育症の患者さんがいることも紹介されていました。生殖医療では科学的根拠の乏しい検査、治療が自費診療として行われることがあります。

不育症が認知され、患者さんが理解することで、医療格差が是正されるかもしれません。

女性の声で治療が変化した疾患に子宮内膜症があります。子宮内膜症はかつて、高価で副作用の多い治療が主流でしたが、今はホルモン剤による治療で高い患者満足度が得られています。女性の声によって〝流産〟も変わる可能性があります。報道の力が患者を助ける、そんな疾患が存在します。

(名古屋市立大産科婦人科教授)

2012.1.16

2011年8月22日毎日新聞　「不育症」患者数　岡崎コホート研究

毎日新聞

MAINICHI

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「不育症」患者140万人

厚労省研究班推計　妊娠経験の4.2%

妊娠はするものの流産や死産を繰り返す「不育症」患者は妊娠経験者の4・2%で発生し、140万人いると推定できることが、厚生労働省研究班の調べでわかった。不育症の発症頻度や患者数の調査は初めて。29日から大阪市で始まる日本産科婦人科学会で報告される。

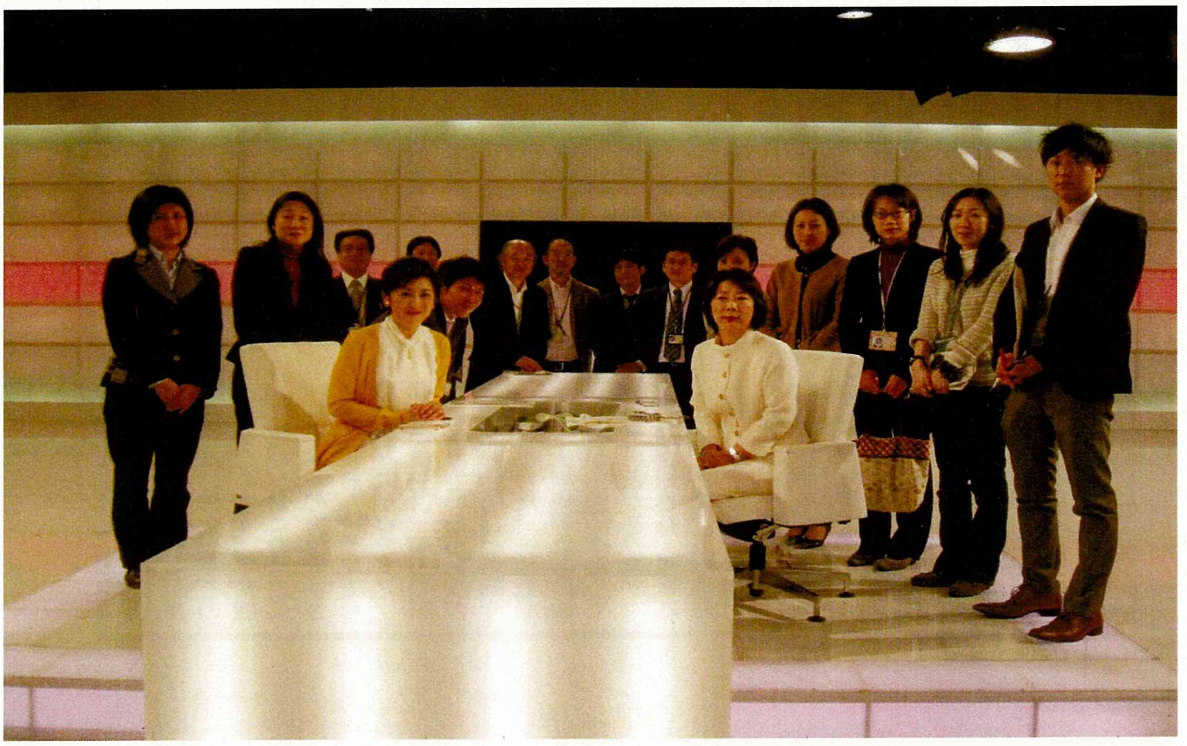
名古屋市立大学が07～10年、愛知県岡崎市で健康診断を受けた35～79歳の女性2733人に尋ねた。妊娠したことのある女性2503人のうち953人(38%)が流産の経験があると回答。研究班は不育症を「2回以上の流産や死産あるいは早期新生児死亡がある場合」と定義しており、2回以上の流産を経験したのは105人、3回以上は22人だった。研究班が07年の人口統計を基に推定すると、不育症は年3万人が発症し、140万人の患者がいるとみられる。

また不育症に該当した105人のうち、9割超の100人が出産しており、名市大の杉浦真弓教授は「流産を重ねても出産している。くじけないでほしい」と話す。不育症の原因は▽子宮の形の異常▽カップルの染色体異常▽血栓で胎児に栄養が届かない――などだが、7割近くは原因不明だ。【五味香織】

◇

23日からくらしナビ面で「こうのとり追って」第3部「不育症」を連載します。

2012年2月14日NHKクローズアップ現代「産みたいのに産めない～卵子老化の衝撃～



平成２３年度厚生労働科学研究費補助金（成育疾患克服等次世代育成基盤研究事業）
分担研究報告書

産科抗リン脂質抗体症候群と抗リン脂質抗体スコア

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研究協力者　大友耕太郎　北海道大学大学院医学研究科免疫・代謝内科学分野

研究要旨
本研究班では、抗リン脂質抗体が不育症の最大のリスクのひとつであるとして、その評価法を検討している。抗リン脂質抗体症候群(APS)の診断にはSapporo分類基準シドニー改変を用いるが、抗体の陰性または陽性の定性的評価のみで、抗体価の大小や抗体の多寡という定量的評価は行われなかった。我々は多数の抗リン質抗体を同時に測定し、それらを一元的に定量化（点数化）した「抗リン脂質抗体スコア（aPL-S)」を定義し、APS診断マーカーとして有用であることを示した。APSは血栓症または妊娠合併症（不育症）が臨床症状であるが、今回はデータベースを用いてaPL-Sが血栓症リスクを示すマーカーとなりうるか、後ろ向き観察研究を行った。対象は2002年から2003年に当科を受診し、抗リン脂質抗体を測定した患者411名。2009年まで後ろ向き追跡し、血栓症について調査を行い、aPL-Sとの関連を調べた。２年以上フォロー可能であった症例は302名(73.4%)であり、平均観察期間は67.7±14.9月であった。期間中に32名が血栓症を、11名が出血合併症を発症した。aPL-Sが30点以上の患者は39名で、うち34例（87%）で抗血栓治療がおこなわれていたにも関わらず、12名（31%）に新規血栓症を認めた。aPL-Sが30点以上の場合、血栓症の相対危険度は5.40[95%CI:2.38-12.23]で有意に高値であった。以上より、aPL-Sは血栓症発症リスクのマーカであり、抗リン脂質抗体症候群の予後を推定させる可能性が示唆された。今後は、このスコアが妊娠合併症のリスクに応用可能かどうか検討する予定である。

A．研究目的

本研究班では、抗リン脂質抗体が不育症の最大のリスクのひとつであるとして、その評価法を検討している。抗リン脂質抗体は多様な自己抗体群である。抗リン脂質抗体症候群（APS）の診断には通常Sapporo分類基準シドニー改変を用いるが、抗体の陰性または陽性の定性的評価のみで、抗体価の大小や抗体の多寡という定量的評価は行われない。一方、感染症や悪性疾患の場合に検出されるループスアンチコアグラントを代表として、抗リン脂質抗体には非特異的な抗体も多く含まれ、「１つかそれ以上の抗リン脂質抗体が陽性」でAPSを定義してしまうことに多くの問題点が指摘されている。そこで、当施設では多数の抗リン脂質抗体を同時に測定し、それらを一元的に定量化（点数化）した「抗リン脂質抗体スコア(aPL-S)」を定義し、APS診断を総合的、定量的に評価する有用なマーカとなることを見出した。

今回、当科のデータベースを用いて、aPL-Sが血栓症リスクを示すマーカとなりうるか、後ろ向き観察研究を行った。

B．研究方法

対象は2002年から2003年に当科を受診し、抗リン脂質抗体を測定した患者411名。2009年まで後ろ向き追跡し、血栓症、出血合併症等について調査を行い、aPL-Sとの関連を調べた。全患者のループスアンチコアグラント（aPTT法、ラッセル蛇毒凝固時間法、カオリン凝固時間法)、IgG/M抗カルジオリピン抗体、IgG/M抗β2-グリコプロテインⅠ(β2-GPⅠ)抗体、IgG/Mホスファチジルセリン依存性抗プロトロンビン抗体を測定し、各患者の「抗リン脂質抗体スコア(aPL-S)」を計算した。2年以上追跡可能な症例を有効症例とした。

（倫理面への配慮）

データベースを用いた後ろ向き研究であり、倫理的な問題は少ない。個人情報については厳重に管理した。

C．研究結果

２年以上フォロー可能であった症例は302名(73.4%)であり、平均観察期間は67.7±14.9月であった。期間中に32名が血栓症を、11名が出血合併症を発症した。aPL-Sが30点以上の患

者は39名で、うち34例（87%）で抗血栓治療がおこなわれていたにも関わらず、12名(31%)に新規血栓症を認めた。aPL-Sが30点以上の場合、血栓症の相対危険度は5.40[95%CI:2.38-12.23]で有意に高値であった。また抗血栓療法を反映して6名（15.4%）に出血合併症を認め、出血合併症の相対危険度は9.38[95%CI:2.71-32.45]であった。

D．考察

aPL-Sは血栓症のリスクを示すマーカとなる可能性が示された。すなわち、aPL-Sが高値の患者群で、観察期間中にあらたに血栓症を発症することが多いことが今回の後ろ向き観察研究で明らかとなった。今回は後ろ向き検討による結果であり、真の予後（リスク）とaPL-Sの関係について論じるためには今後の前向き検討が必要である。本スコアを普及させ、一般診療に応用するためには、個々の抗リン脂質抗体検査の標準化が必要なことはいうまでもなく、コストや汎用性と効率を考えたスコア自体の再編も必要と考えている。

今回の検討では、妊娠合併症を観察期間中に発症した例はなかった。今後は、妊婦を対象に本スコア、または改変スコアを用いて、妊娠合併症リスクを反映する評価法を確立する予定である。

E．結論

aPL-Sは血栓症発症リスクのマーカであり、抗リン脂質抗体症候群の予後を推定させる可能性が示唆された。妊娠合併症のリスクについて、今後の検討を要する。

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H.知的財産権の出願・登録状況
（予定を含む）
1. 特許取得
なし
2. 実用新案登録
なし
3. その他
なし

研究成果の刊行に関する一覧表

書籍

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Ioannou Y, Zhang JY, Qi M, Gao L, Qi CJ, Yu DM, Lau H, Sturgess AD, Vlachoyiannopoulos PG, Moutsopoulos HM, Rahman A, Pericleous C, Atsumi T, Koike T, Heritier S, Giannakopoulos B, Krilis SA.	Novel assays of thrombogenic pathogenicity for the antiphospholipid syndrome based on the detection of molecular oxidative modification of the major autoantigen beta2-glycoprotein I.	Arthritis Rheum	63	2774-82	2011
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Otomo K, Atsumi T, Amengual O, Fujieda Y, Kato M, Oku K, Horita T, Yasuda S, Koike T.	The efficacy of Antiphospholipid Score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events.	Arthritis Rheum			in press
Hirakawa E, Saito K, Hirata S, Atsumi T, Koike T, Tanaka Y.	A case of catastrophic antiphospholipid antibody syndrome complicated withsystemic lupus erythematosus, double positive for anti-cardiolipin/ß(2) glycoprotein I and anti-phosphatidylserine/prothrombin autoantibodies.	Mod Rheumatol			in press
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Uterine Anomaly and Recurrent Pregnancy Loss

Mayumi Sugiura-Ogasawara, M.D., Ph.D.,[1] Yasuhiko Ozaki, M.D., Ph.D.,[1] Kinue Katano, M.D., Ph.D.,[1] Nobuhiro Suzumori, M.D., Ph.D.,[1] and Eita Mizutani, M.D.[1]

ABSTRACT

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus. Bicornuate and septate uterine have a negative impact on reproductive outcomes and are associated with subsequent euploid miscarriage. The impact of an arcuate uterus on pregnancy outcome remains unclear. There are no definitive criteria to distinguish among the arcuate, septate, and bicornuate uteri. The American Fertility Society classification of Müllerian anomalies is the most common standardized classification of uterine anomalies. According to estimates, 65 to 85% of patients with bicornuate or septate uteri have a successful pregnancy outcome after metroplasty. However, 59.5% of the patients with such anomalies have a successful subsequent pregnancy without surgery, with a cumulative live birthrate of 78.0%. There is no case-control study to compare live birthrates in women who had surgery compared with those who did not. Strict criteria to distinguish between the bicornuate and septate uterus should be established. Further study is needed to confirm the benefits of metroplasty.

KEYWORDS: Bicornuate uterus, congenital uterine anomaly, recurrent pregnancy loss, septate uterus

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus.[1–6] The impact of an arcuate uterus on the occurrence of pregnancy loss remains unclear. The American Fertility Society classification of Müllerian anomalies is the most common standardized classification of uterine anomalies.[7] Office hysteroscopy, hysterosalpingography (HSG), and/or two-dimensional (2D) ultrasound can be used as an initial screening tool. Combined hysteroscopy and laparoscopy, sonohysterography, and three-dimensional (3D) ultrasound can be used for a definitive diagnosis. However, there are no established criteria to distinguish among arcuate, septate and bicornuate uteri.

According to estimates, 65 to 85% of patients with bicornuate or septate uteri have a successful pregnancy outcome after metroplasty.[8–20] In the study by Sugiura-Ogasawara et al on the live birthrate in the absence of surgery, 59.5% of the patients with such anomalies had a successful first pregnancy after the examination as compared with 71.7% of the subjects with normal uteri ($p = 0.084$), and there was no difference in the cumulative live birthrate (78.0% versus 85.5%, respectively).[3] Congenital uterine anomalies have a negative impact on reproductive outcomes; they

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Recurrent Early Pregnancy Loss; Guest Editor, Mary D. Stephenson, M.D., M.Sc.

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ISSN 1526-8004.

are being associated with further euploid (46, XX or 46, XY) miscarriage.[3]

There is no case-control study to compare live birthrates in women who had surgery compared with those who did not. Further study is needed to confirm the benefits of metroplasty.

DIAGNOSTIC CRITERIA FOR CONGENITAL UTERINE ANOMALIES

Uterine development involves three main stages[21,22]:

1. Organogenesis: development of both Müllerian ducts.
2. Fusion: the Müllerian ducts fuse at the lower end to form the upper vagina, cervix, and uterus (lateral fusion).
3. Septal absorption: after the Müllerian ducts fuse, the central septum starts to resorb at ~9 weeks, eventually leaving a single uterine cavity and cervix.

Congenital uterine anomalies may arise from malformations at any step of the Müllerian developmental process.[23] Buttram and Gibbons first proposed a classification of congenital uterine anomalies based on the degree of failure of the Müllerian ducts to develop normally, and they divided them into groups with similar clinical manifestations.[24]

This was revised by the American Fertility Society classification of Müllerian anomalies, which is currently considered the standard classification.[7] The classification has also been modified by a frequently used scheme by Strassmann.[25] The reason for providing the classification is its value to the practicing physician. The American Fertility Society classification is limited in that it does not specify the diagnostic methods or criteria that should be used to diagnose the anomalies and is based on the subjective impression of the clinician performing the evaluation. The committee had difficulty in deciding how to include arcuate uterus. The arcuate uterus could be classified as a form of a incomplete septate uterus because it is externally unified. However, the committee also proposed that the arcuate uterus could be classified separately because it appears to behave in a more benign fashion.

HSG is the most frequently used modality for the diagnosis of congenital anomalies; however, when used alone, it cannot distinguish between a septate and a bicornuate uterus.[7,25] Thus hysteroscopy/laparoscopy, which allows examination of both the uterine cavity and the external uterine contour, can precisely ascertain the uterine anomaly in accordance with the American Fertility Society classification of Müllerian anomalies.

It has been reported that an angle <75 degrees between the uterine horns is suggestive of a septate uterus and that an angle >105 degrees is indicative of a bicornuate uterus.[21,26] Tompkin's index has also been used to distinguish between arcuate uterus and an incomplete septate or bicornuate uterus.[27] A Tompkin's index >25% is considered to be consistent with the diagnosis of a septate or bicornuate uterus.

The advent of sonohysterography,[28] magnetic resonance imaging (MRI)[29] and 3D ultrasound now allows more accurate differential diagnosis,[30] although distinguishing an arcuate from a incomplete septate or bicornuate uterus still remains difficult. Troiano and McCarthy and Fedele et al considered a uterus to be septate rather than double (bicornuate or didelphys) in the presence of a fundal distal border indentation of ≤ 5 mm above the line joining the two ostia (interostial line).[26,31] Woelfer et al provided new 3D ultrasound criteria and indicated that a bicornuate uterus can be distinguished from a septate uterus when the fundal indentation dividing the two cornua was >10 mm.[30] According to a 3D ultrasound investigation, the incidence of the septate uterus is higher. Letterie and Wu et al also consider the uterus to be septate when the fundal indentation is <10 mm below the interostial line.[21,32] These criteria are useful for making a decision on transcervical resection (TCR) for a uterine septum.

Hysteroscopy allows direct visualization of the uterine cavity and ostia. It is therefore an accurate tool for identifying congenital uterine anomalies and is often used to establish a definitive diagnosis after an abnormal finding. Some authors consider the combination of hysteroscopy and laparoscopy to be the gold standard.[21,33–35] Based on a systematic review, Saravelos et al concluded the most accurate diagnostic procedures are combined hysteroscopy and laparoscopy, sonohysterography, and 3D ultrasound.[36] Preliminary studies suggest that MRI is a relatively sensitive tool. HSG and/or 2D ultrasound are used as initial screening tools.

Acién suggested the diagnosis of a bicornuate uterus is made when the external contour of the uterus at laparoscopy reveals any visible depression in the midline, associated with overall widening of the fundus.[37] The prevalence of bicornuate uterus may be higher if Acién's classical criteria are used; likewise, the prevalence of a uterine septum may be higher if the criteria of Fedele or Woelfer et al are used. It remains difficult to distinguish among arcuate, incomplete septum, and incomplete bicornuate uterus.

Distinction between bicornuate uterus and uterine septum is important for selecting appropriate treatment. However, the clinical significance of the distinction still remains unclear.

PREVALENCE OF MAJOR MALFORMATIONS

The frequency of congenital uterine anomalies has been reported to vary between 1.8% and 37.6% in women with

a history of recurrent miscarriage. The variation largely depends on the methods and the criteria selected for the diagnosis.[1–6]

Recurrent miscarriage traditionally was defined as three or more consecutive miscarriages occurring before 20 weeks postmenstruation.[38] However, such terminology is not uniformly accepted in studies, which may also influence the results. Because the terminology is so divergent, the following definitions are used in this article:

Recurrent early pregnancy loss: two or more miscarriages at <10 weeks of gestation.
Recurrent pregnancy loss: two or more pregnancy losses at any gestational age.
Recurrent early miscarriage: three or more consecutive miscarriages at <10 weeks of gestation.
Recurrent miscarriage: three or more consecutive miscarriages at <20 to 28 weeks of gestation (to include European publications)

Table 1 shows the incidence of uterine anomalies based on some studies that included ≥500 cases. Raga et al described that patients (6.3%; 54 of 868; $p < 0.05$) with a history of two or more consecutive pregnancy losses had a significantly elevated incidence of Müllerian anomalies in comparison with patients who were fertile (3.8%; 49 of 1289) or infertile (2.4%; 25 of 1024) cases.[1] The prevalence of arcuate uterus in this study was 1.0%, 1.6%, and 1.1%, respectively. Because arcuate uterus seems to be a normal variant, the incidence of major anomalies was 5.3% in this study. The diagnoses in the patients were confirmed by HSG and laparoscopy/laparotomy during the years 1980 to 1995.

Makino et al reported an incidence of uterine anomalies of 15.7% (188 of 1200) using HSG in 1992.[2] Of the 188, 133 (70.7%) had an arcuate uterus. The incidence of major anomalies was 4.6% (55 of 1200) in patients with two or more consecutive pregnancy losses.

In the study by Sugiura-Ogasawara et al, major malformations such as septate, bicornuate or unicornuate uterus, and didelphys were found in 3.2% of the patients.[3]

Several studies have reported that the prevalence of septate uterus is higher than that of bicornuate uterus. However, Lin et al concluded from a literature review that bicornuate, septate, arcuate, unicornuate, and didelphys uteri occurred at a prevalence of 37%, 22%, 15%, 4.4%, and 11%, respectively.[39] Our study, based on Acién's criteria, also indicated that bicornuate uterus occurs at the highest prevalence. Lin et al also concluded that arcuate uterus has little adverse impact on the reproductive outcome.

Based on a systematic review, Saravelos et al concluded the prevalence of congenital uterine anomalies was 6.7% in the general population, 7.3% in a

Table 1 Prevalence of Congenital Uterine Anomalies in Recurrent Pregnancy Loss

	n	Age Yrs (SD)	Bicornuate	Septate	Arcuate	Unicornuate	Didelphys	Total, Excluding Arcuate	Evaluation	RPL Definitions
Suigiura-Ogasawara et al, 2010[3]	1676	31.5 (3.5)	2.3%	0.6%	–	0.3%	0.1%	3.2%	HSG, laparoscopy, MRI	Two or more pregnancy loses
Salim et al, 2003[6]	509	34.9	1.2%	5.3%	16.9%	0.4%	0%	6.9%	TVS, 3D, US	Three or more unexplained first trimester
Raga et al, 1997[1]	868	28	1.9%	2.0%	1.0%	0.6%	0.7%	5.3%	HSG, laparoscopy	Two or more pregnancy losses
Clifford et al, 1994[4]	500	32.9	0.6%	1.2%	–	–	–	1.8%	US	Three or more miscarriages
Makino et al,1992[2]	1200	31.4	–	4.1%	11.1%	0.4%	–	4.6%	HSG	Two or more pregnancy losses
Saravelos et al, 2008[36] (review)	1257	–	1.0%	5.0%	12.2%	0.4%	0.1%	3.9%	Hysteroscopy, laparoscopy, SHG, 3D US	Three or more miscarriages

RPL, recurrent pregnancy loss; HSG, hysterosalpingography; MRI, magnetic resonance imaging; TVS, transvaginal sonography; 3D, three dimensional; US, ultrasound; SHG, sonohysterography.

population of women with infertility, and 16.7% in a population with recurrent miscarriages.[36] The prevalence of an arcuate uterus in the three cohorts was 4.9%, 1.9% and 12.2%, respectively. Thus the prevalence of major anomalies in the three cohorts was 1.8%, 5.4%, and 4.5%, respectively. Saravelos et al concluded that arcuate uterus has a possible association with miscarriage because the prevalence in patients with recurrent miscarriages was higher than that in the general population.

Women with recurrent pregnancy loss have a 3.2 to 6.9% likelihood of having a major uterine anomaly and a 1.0 to 16.9% chance of having an arcuate uterus.[1–6] However, the impact of the arcuate uterus on miscarriage remains unclear.

MECHANISMS TO EXPLAIN THE ADVERSE EFFECTS OF UTERINE ANOMALIES ON RECURRENT PREGNANCY LOSS

The diminished size of the uterine cavity, as well as cervical incompetence, have been suggested as possible etiological factors.[40] The most widely accepted theory is that the septum consists of fibroelastic tissue with inadequate vascularization and altered relations between myometrial and endometrial vessels that exert a negative effect on fetal placentation.[40–43] Fedele et al suggests that the risk of miscarriage is related to the site of septal implantation.[43] Dabirashrafi et al found a significantly lower amount of connective tissue, higher amount of muscle tissue, and more vessels in the uterine septum.[44] Raga et al compared the mRNA expressions of vascular endothelial growth factor (VEGF) receptors in different endometrial locations of septate and normal uteri, and they suggest that a local defect of VEGF transmembranous receptor (KDR and Flt-1) expression in the endometrium covering the septal area may be responsible for recurrent pregnancy loss.[45]

Our previous clinical study results lend support to these suggested mechanisms.[3] The height of the defect/length of the remaining uterine cavity (defect/cavity [D/C]) ratio was calculated in cases of bicornuate and septate uteri and compared between patients having miscarriages and giving live births at the subsequent first pregnancy. We attempted to determine whether the D/C ratio might have a predictive value for further miscarriage in recurrent pregnancy loss cases. The mean values (standard deviation [SD]) of the D/C ratio in the miscarriage and live birth groups were 0.8332 (0.3974) and 0.4776 (0.2745), respectively ($p = 0.0057$; 95% confidence interval [CI], 0.1115 to 0.5998). When two patients with noneuploid miscarriages were excluded, the D/C ratio in the miscarriage group was found to be significantly higher than that in the live birth group ($p = 0.0051$).

From the receiving operating characteristic (ROC) curve, the cutoff value of the ratio was determined to be somewhere between 0.59 and 0.64, yielding the highest sensitivity and specificity at a value around 0.75 to 0.80. The area under the ROC curve, that is, the overall total diagnostic accuracy of the D/C ratio for live birth, was 0.808. From the logistic regression, a high D/C ratio was found to be an independent risk factor for failure of live birth after adjustment for age and number of previous miscarriages. The odds ratio for 0.1 increment of the D/C ratio was 1.42 (95% CI, 1.06 to 1.91).

In 2003, Salim et al found no significant difference in the relative frequency of various anomalies or depth of fundal distortion as determined by 3D ultrasound between women with and without a history of recurrent miscarriages, although abnormalities in uterine anatomy were more severe in women with a history of recurrent miscarriages.[6] In this context, the finding in our previous study that a high D/C ratio may be a predictor of further miscarriage in recurrent cases is clearly of interest.

Surgery

Affected patients are offered surgery in an attempt to restore the uterine anatomy. The first surgery for double uterus was the simple removal of the septum, performed by Ruge and Schroeder in 1882.[8] Strassmann reported vaginal metroplasty for bicornuate uterus.[9] His son, E.O. Strassmann, reviewed 128 cases, including 5 of his own, treated by plastic unification through the abdomen.[25] He described that the indications of unification were "habitual abortion" and "sterility" and that 85.6% of the postoperative pregnancies went through to full term, whereas only 3.7% of the preoperative pregnancies had lasted through to full term. However, he also described that 25 to 40% of women with a double uterus had no disturbances and did not need surgery. The Jones and Jones operation was reported in 1953.[10] They recommended surgery only when adequate investigation reveals no other causes for the recurrent miscarriage.

Table 2 summarizes the live birthrates after surgery in studies including a relative large number of subjects. Makino et al reported that 71 patients underwent modified metroplasties.[2] They found 84.8% (39 of 46) of postoperative pregnancies resulted in live births, whereas none of the 233 presurgical pregnancies were successful. The outcomes of the remaining 25 patients who underwent metroplasty remain unclear.

Candiani et al reported that among 102 cases with recurrent miscarriage and 42 with primary infertility, 68% (45 of 66) of the patients with a septate uterus and 76% (50 of 66) of the patients with a bicornuate uterus who underwent abdominal metroplasty had a successful pregnancy outcome.[11] Ayhan et al reported that among the 89 cases with recurrent miscarriage or preterm delivery, 65% (30 of 46) of the patients with a septate uterus and 83% (45 of 54) of the patients with a

Table 2 Live Birthrate after Metroplasty in Patients with Recurrent Pregnancy Loss Associated with Congenital Uterine Anomalies

	No. of Patients	Type of Anomaly	Method of Surgery	Indication	Live Birthrate Per Pregnancies
Candiani et al, 1990[11]	144	73 septate, 71 bicornuate	Tompkins, Jones, TeLinde, Strassmann	Recurrent miscarriage	Septate 45/66 (68%) Bicornuate 50/66 (76%)
Ayhan et al, 1992[12]	89	49 septate, 40 bicornuate	Tompkins, Jones, Strassmann	Recurrent miscarriage and preterm delivery	Septate 30/46 (65%) Bicornuate 45/54 (83%)
Makino et al, 1992[2]	71	Arcuate, septate	Abdominal	Recurrent miscarriage	39/46 (84.8%)
DeCherney et al, 1986[15]	72	Septate	Resectoscope	Recurrent miscarriage	58/72 (80%)
Daly et al, 1989[16]	55	Septate	Scissors	Recurrent miscarriage and preterm delivery	60/75 (80%)
Hickok, 2000[18] (review)	40	Septate	Resectoscope	Pregnancy loss or complication of pregnancy (28); infertility (10)	17/22 (77.3%)
Kormanyos et al, 2006[20]	94	Septate	Resectoscope	Two or more miscarriages	33/48 (68.8%)

bicornuate uterus had a successful pregnancy outcome.[12] However, the studies had no controls and the patients who did not become pregnant were not mentioned, hence infertility following surgery was not addressed.

Surgery via the transvaginal route for septate uterus was initially proposed by Ruge in 1882.[8] Edstrom performed the first hysteroscopic removal of the septum in 1974.[46] Chervenak and Neuwirth reported the live birthrate after hysteroscopic metroplasty.[13] Hysteroscopic surgery is accepted worldwide because of its advantages over other conventional abdominal procedures.[14–20] The primary advantage is the avoidance of laparotomy. The anesthesia time and recovery time are also shortened, the risk of infection is greatly reduced, the contraceptive duration for the subsequent pregnancy is shortened, and uterine incision is avoided, which means that the patients can be given a trial of vaginal delivery rather than be required to undergo a cesarean delivery.

Goldenberg et al described that the pregnancy wastage in women with recurrent miscarriage who underwent hysteroscopic resection of an intrauterine septum decreased from 87.5% to 44.4% postoperatively and that hysteroscopic resection of an intrauterine septum may benefit patients suffering from recurrent pregnancy wastage.[14] Hickok reported a preoperative pregnancy loss rate of 77.4%, a miscarriage rate of 18.2%, and an uncomplicated delivery rate of 77.3% after hysteroscopic septum resection.[18] Kormányos et al compared the pregnancy outcomes after removal of a septum between cases with and without a residual septum among patients with a history of two or more miscarriages, and they concluded that the live birthrate in cases with no remnant septum was significantly higher than that in the cases with a remnant septum.[20] However, the live birthrate in patients undergoing the first hysteroscopy was 35.1% (33 of 94) and the cumulative live birthrate after one or two removals was 54.3% (51 of 94).

EVIDENCE LEVELS OF STUDIES ON RECURRENT PREGNANCY LOSS ASSOCIATED WITH AN UTERINE ANOMALY

Surgical techniques to enlarge the uterine cavity have advanced. Almost all studies have compared the live birthrate between before and after surgery.[14–20] However, it is inappropriate to simply make comparisons before and after surgery because the prior miscarriage rate is usually 100%, but the subsequent success rate is never 0% in primary recurrent miscarriage. The subsequent live birthrate is expected to be 72% in patients with unexplained recurrent pregnancy loss in the absence of abnormal chromosomes in either partner, and it also decreases with the previous number of losses.[47,48] In the absence of a randomized trial, the subsequent live birthrate should be compared prospectively in patients with recurrent miscarriage associated with a uterine anomaly, treated and not treated with surgery. To date, there have been no prospective studies of this kind.

SUBSEQUENT PREGNANCY OUTCOMES IN PATIENTS WITH RECURRENT PREGNANCY LOSS CAUSED BY CONGENITAL UTERINE ANOMALIES IN THE ABSENCE OF SURGERY

Information concerning the prognosis of patients with congenital uterine anomalies not treated by surgery is limited. We conducted a case-control study of 1676 patients with a history of two or more (2 to 12)

consecutive miscarriages whose subsequent pregnancies were ascertained at least one time in our medical records between 1986 and 2007 at Nagoya City University Hospital.[3] HSG, chromosome analysis for both partners, determination of antiphospholipid antibodies (aPL), including lupus anticoagulant and $\beta 2$ glycoprotein I dependent anticardiolipin antibodies, and blood tests for hypothyroidism, diabetes mellitus, and hyperprolactinemia were performed in all patients before the subsequent pregnancy.

The pregnancy outcomes of all 1676 patients were examined. Of the total, 94 who had structural chromosomal abnormalities, including 73 translocations, in either partner, were excluded from the analysis; 75 patients exhibited persistent aPL and were treated by combined low-dose aspirin and heparin therapy.

Of the total, 54 (3.2%) had congenital uterine anomalies, including 38 with partial bicornis unicolli, 10 with uterine septum, 5 with unicornis, and 1 with didelphys. None had hypoplasia/agenesis or diethylstilbestrol (DES) drug-related anomalies. Two patients, one with a uterine septum and one with a bicornuate uterus, also had translocations in either partner.

We compared the pregnancy outcomes between the 42 patients with septate or bicornuate uteri not undergoing surgery and the 1528 patients without uterine anomalies or abnormal chromosomal karyotype in either partner. We found no differences in the baseline characteristics between the two groups.

Table 3 summarizes the subsequent pregnancy outcomes; 25 of the 42 patients with a septate or bicornuate uterus (59.5%) not treated with any kind of surgery had a successful outcome, compared with 1096 of the 1528 patients (71.7%) without a congenital uterine anomaly ($p = 0.084$). One patient underwent surgery after a further miscarriage. Thus, 32 of the 41 (78.0%) patients and 1307 of the 1528 (85.5%) patients with and without uterine anomalies could cumulatively have a live baby within the follow-up period, not significant. Live birth rates of patients with congenital uterine anomalies tended to be lower both at the first pregnancy after ascertainment, and cumulatively.

Furthermore, the abnormal chromosomal karyotype rates in the miscarriages in cases with and without uterine anomalies were 15.4% (2 of 13) and 57.5% (134 of 233), respectively, at the first pregnancy after ascertainment of uterine anomalies. The difference was highly significant ($p = 0.006$).

One of five patients with a unicornuate uterus succeeded in having an infant at the first pregnancy after evaluation, and four of five had an infant cumulatively. The patient with didelphys also succeeded at the first pregnancy after evaluation.

The benefits of surgical correction (open and hysteroscopic) on the pregnancy outcomes have yet to

Table 3 Successful Reproductive Outcomes after Diagnosis of Uterine Anomalies in Patients with Recurrent Pregnancy Loss

	Live Birthrates (% of Pregnancies)						Cumulative Live Birthrates (% of Couples)			
	With Anomalies ($n = 42$)	Bicornuate	Septum	Without Anomalies ($n = 1528$)	Difference in %	p Value	With Anomalies ($n = 41$)*	Without Anomalies ($n = 1528$)	Difference in %	p Value
Pregnancy after uterine anomaly was ascertained										
1st	25/42 (59.5%)[†]	21/37 (56.8%)	4/5 (80.0%)	1096/1526 (71.7%)	−12.2	0.084	25 (61.0%)	1096 (71.7%)	−10.7	0.133
2nd	5/9 (55.6%)	4/8 (50.0%)	2/2 (100%)	166/275 (60.4%)[‡]	−4.8	0.772	30 (73.2%)	1262 (82.6%)	−9.4	0.119
3rd	2/2 (100%)	2/2 (100%)	–	38/69 (55.0%)	+45.0	0.207	32 (78.0%)	1300 (85.1%)	−7.1	0.215
4th				4/18 (22.2%)				1304 (85.3%)		
5th				3/9 (33.3%)				1307 (85.5%)		
6th				0/6 (0%)				1307 (85.5%)		
Final follow up	–			–			32 (78.0%)	1307 (85.5%)	−7.5%	

Adapted from Sugiura-Ogasawara et al, 2010.[3]
*One patient underwent surgery between the first and second pregnancy after the confirmation of an anomaly; thus this case was excluded from the cumulative analysis.
[†]Comparison was performed between patients with uterine anomalies and normal uteri.
[‡]Patients who had a successful first pregnancy were excluded from the analysis of the second and subsequent pregnancies.

be assessed in a randomized trial. However, the D/C ratio might be useful for an appropriate selection of patients. Comparison of cases of anomalies treated and not treated by surgery is urgently needed in women with a history of recurrent pregnancy loss.

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Management of Recurrent Pregnancy Loss Associated with a Parental Carrier of a Reciprocal Translocation: A Systematic Review

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ABSTRACT

This study reviews systematically the effectiveness of management strategies for carriers of a reciprocal translocation involving two chromosomes, ascertained on the basis of recurrent pregnancy loss. Subsequent pregnancy outcomes were tabulated based on whether management was medical or involved in vitro fertilization/preimplantation genetic diagnosis (IVF/PGD). A total of 129 cases from 13 articles met the criteria, of which 89% were managed medically. Before management, the overall live birthrate was 4% (19 of 484 pregnancies). Management was medical in 109 cases and IVF/PGD in 20 cases. Cumulative live birthrate was 74% (81 of 109 cases) in the medical management group and 35% (7 of 20) in the IVF/PGD group. Based on this systematic review, successful pregnancy outcomes are high following either medical management or IVF/PGD for carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss. But it is difficult to compare outcomes directly for these two strategies because of the different end points reported. Understanding the differences is essential for effective counseling. Until a well-designed study comparing the two strategies is performed, or at least prospective cohort studies with strict entry criteria and definitions, the cumulative experience and success of both medical management and IVF/PGD must be used to counsel patients who are carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss.

KEYWORDS: Reciprocal translocation, recurrent pregnancy loss, recurrent miscarriage, in vitro fertilization, preimplantation genetic diagnosis

Recurrent pregnancy loss (RPL), defined as two or more miscarriages <20 weeks of gestation, affect ~5% of couples trying to establish a family.[1] It is a devastating reproductive problem with, unfortunately, few evidence-based treatment options.

Evaluation of recurrent pregnancy loss should be individualized, based on the pattern of presentation, the gestational ages at time of miscarriage, and cytogenetic results of miscarriages.[2] The prevalence of parental carriers of a structural chromosome rearrangement,

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most often a reciprocal or Robertsonian translocation, accounts for 2.5 to 7.8% of couples with RPL.[2–6] How often miscarriages in carriers of a structural chromosome rearrangement are due to errors in meiosis involving affected chromosomes, resulting in unbalanced rearrangements, is unfortunately not well documented because miscarriages are not routinely sent for chromosome testing. Stephenson and Sierra reported that 36% of miscarriages are unbalanced, based on a cohort of 51 carriers of a structural chromosome rearrangement, ascertained on the basis of recurrent pregnancy loss.[7]

Management of parental carriers of a reciprocal translocation, ascertained on the basis of RPL, remains controversial. Thus the objective of this systematic review was to compare subsequent pregnancy outcomes in carriers of a reciprocal translocation, ascertained on the basis of RPL, who were managed medically or with in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) and preimplantation genetic diagnosis (PGD). The results of this systematic review may be useful for counseling such patients because it summarizes the cumulative experience and success of both medical management and IVF/PGD. With this information, carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss, can make an informed decision on the management of subsequent pregnancies.

MATERIAL AND METHODS

A literature search was performed using PubMed, restricted to English-language articles published from January 1990 to December 2010, using the terms "*recurrent* or *repeated miscarriage* or *pregnancy loss* or *spontaneous abortion* or *embryonic demise* or *fetal demise*, or *habitual abortion*, combined with *reciprocal translocation, translocation,* or *structural chromosome rearrangement or abnormality*" An additional search was done combining all of these combinations with *preimplantation genetic diagnosis.* All original research articles were reviewed; abstracts were excluded. Further articles were obtained from references. Individual cases that met criteria were extracted.

Inclusion criteria were (1) history of recurrent pregnancy loss, defined as two or more miscarriages <20 weeks of gestation, (2) one of the partners was a carrier of a reciprocal translocation involving two chromosomes and either partner had no other structural chromosome rearrangement, and (3) obstetric history, subsequent management, and outcomes were described. In the medical management group, only cases with at least one subsequent outcome were included. In the IVF/PGD group, all cases with at least one cycle outcome were included.

The following articles were excluded because carriers of a reciprocal or a Robersonian translocation could not be differentiated: Goddijn et al, 2004; Carp et al, 2004; Franssen et al, 2006; and Fischer et al, 2010.[3,8–10] The articles by Verlinsky et al, 2005; Otani et al, 2006; and Ozawa et al, 2008, were excluded because they did not provide individual obstetric histories.[11–13] Escudero et al, 2008, and Lim et al, 2008, were excluded because the couples, in addition to carrier of a reciprocal translocation, had other structural chromosome rearrangements, including Robertsonian translocations and inversions.[14,15]

Cases were grouped according to the type of subsequent management, either "medical" or IVF/PGD. "Medical management" consisted of evaluation and management of concomitant factors, followed by "close monitoring," as defined by the individual study.

Pregnancy was defined according to the study and generally differed between the two management groups. With medical management, pregnancy was defined by a positive human chorionic gonadotropin (hCG). With IVF/PGD, pregnancy was usually defined by the presence of a gestational sac on ultrasound.

The primary outcome was defined as an ongoing pregnancy of at least 20 weeks gestation, which was assumed to be a live birth. The secondary outcome was defined as chromosome results of either miscarriages or ongoing pregnancies.

RESULTS

Approximately 358 articles were identified using the terms previously described. Of these, 13 articles had at least one case that met the criteria.[4,5,7,15–25] A total of 129 parental carriers of a reciprocal translocation, ascertained on the basis of recurrent pregnancy loss, were found. Table 1 reports the obstetric histories of 109 cases with subsequent medical management. Table 2 reports the obstetric histories of 20 cases with subsequent IVF/PGD management.

The sex of the reciprocal translocation carrier was reported in all cases; 61% ($n = 79$) were female, and 39% ($n = 50$) were male. Of the female carriers, 65 were from the medical management group and 14 from the IVF/PGD group. The specific chromosomes involved in the reciprocal translocations were reported in 76 of the 79 female carriers. In the female carriers, chromosome 2 was the most frequent chromosome involved in the reciprocal translocations ($n = 16$), followed by chromosome 6 ($n = 14$); chromosome 1 ($n = 12$); chromosome 7 ($n = 11$); chromosome 4 ($n = 10$); chromosome 10 ($n = 9$); chromosomes 1, 8, and 14 ($n = 8$, each); chromosome 18 ($n = 7$); chromosomes 5, 12, and 15 ($n = 6$, each); chromosomes 3, 9, 15, and 17 ($n = 5$, each); chromosome 22 ($n = 3$); chromosomes 13, 20, and 21 ($n = 2$, each); and chromosomes 16 and 19 ($n = 1$, each).

In the male carriers, 44 were from the medical management group and 6 from the IVF/PGD group. The specific chromosomes involved in the reciprocal

Table 1 Carriers of a Reciprocal Translocation with a History of Recurrent Pregnancy Loss, with Subsequent Medical Management ($n = 109$)

Carrier Status	Prior Pregnancies	Subsequent Pregnancies
Sugiura-Ogasawara et al, 2004[5]		
46, XX, t(2p;6p)	SA, SA, SA, SA	Term (balanced 46, XX, t(2p;6p)mat)
46, XX, t(6;10)(q23;p13)	SA, SA	SA (unbalanced 46, XX, der(10)t(6;10)(q23;p13)mat)
46, XX, t(3;5)(q23;q33.3)	SA, SA, SA	SA (unbalanced 47, XX, +der(3)t(3;5)(q23;q33.3)mat, der(5)t(3;5)(q23;q33.3)mat), SA, Term (46, XX)
46, XX, t(4;14)(q21.2;p11.2)	SA, SA, SA	Term (46, XY), **Success (46, XX)**
46, XX, t(5;9)(q31.1;q34.3)	SA, SA	SA (47, XX, +22), **IUFD at 38 wk (46, XY), SA,SA (unbalanced 46, XY, 8q+), SA (unbalanced 46, XY, +9(q32)), Term (balanced 46, XX, t(5;9)(q31.1;q34.3)mat)**
46, XX, t(6;8)(q25.1;q11.2)	SA, SA, SA	Term (46, XY), **Term (46, XX)**
46, XX, t(8;11)(q21;q13)	SA, SA	Term (balanced 46, XY, t(8;11)(q21;q13)mat), **Term (46, XX)**
46, XX, t(2;7)(p21;15)	SA, SA	SA
46, XX, t(4;6)(q31.1;q15)	SA, SA	SA (unbalanced 46, XX, der(6)t(4 ;6)(q31.1;q15)mat), SA, Term (balanced 46, XX, t(4;6)(q31.1;q15)mat)
46,XX, t(17;18)(p11.5;p11.2)	SA, SA, SA, SA, SA, SA	SA (unbalanced 46, XX, der(18)t(17;18)(p11.5;p11.2)mat), SA, SA, SA (unbalanced 46, XX, der(18)t(17 ;18)(p11.5 ;p11.2)mat), SA, SA, SA, **Preterm, SA**
46, XX, t(11;13)	SA, SA, SA	SA
46, XX, t(2;15)(p23;q15)	SA, SA, SA	SA (46, XX), SA (balanced 46, XX, t(2;15)(p23;q15)mat)
46, XX, t(3;7)(q27;p22)	SA, SA	SA, Term, **Success**
46, XX, t(2q-;8q+)	SA, SA, SA, SA	SA (48, XY, +16, +21), SA, SA, SA, Term (46, XX)
46, XX, t(8;20)(p21;p11.2)	SA, SA, SA, SA	SA, SA, SA (46, XX), SA, SA (46, XX), SA (46, XX), **Preterm** (balanced 46, XY, t(8;20)(p21;p11.2)mat), Term (balanced 46, XX, t(8;20)(p21;p11.2)mat), **Success**
46, XX, t(6;7)(q25.1;q21.2)	SA, SA, SA	SA
46, XX, t(1;6)(q44;q21)	SA, SA, SA, SA	SA (unbalanced 46, XX, der(1)t(1;6)(q44;q21)mat), Term (balanced 46, XY, t(1;6)(q44;q21)mat), **Term**
46, XX, t(4;11)(q35;q13.3)	SA, SA, SA	SA (unbalanced 46, XY, -4, +der(4)), SA, Term
46, XX, t(1;4)(q42.3;p12)	SA, SA, SA, SA	Term
46, XX, t(2;11)(q37;q13.1)	SA, SA	Term
46, XX, t(10;13)(q24.3;q21.2)	SA, SA	SA, SA (unbalanced 46, XX, der(10)t(10;13)(q24.3;q21.2)mat), SA (46, XX), Term (46, XX)
46, XX, t(11;22)(q23.3;q11.2)	SA, SA	SA (unbalanced 48, XX, +16, +der(22)t(11;22)(q23.3;q11.2)mat,), Term (balanced 46, XY, t(11;22)(q23.3;q11.2)mat)
46, XX, t(2;5)(q35;q35.3)	SA, SA	SA
46, XX, t(3;15)(q13.2;q21.2)	SA, SA	SA, **Term**
46, XX, t(12;17)(q24.1;p12)	SA, SA, SA	Term (46, XX)
46, XX, t(11;15)(p10;q10)	SA, SA, SA, SA, SA	SA, SA
46, XY, t(10p;13q)	SA, SA	SA (hydatidiform mole), Term (46, XX)
46, XY, t(lq;3q)	SA, SA	Term (balanced 46, XY, t(lq;3q)pat), Term (balanced 46, XY, t(lq;3q)pat), **Term (balanced 46, XY, t(lq;3q)pat)**
46, XY, t(11;15)(p11;p11)	SA, SA, **SA (balanced 46, XX, t(11;15)(p11;p11)mat)**	SA (unbalanced 46, XY, der(15)t(11;15)(p11;p11)pat)
46, XY, t(10;15)(q26.1;q22.1)	SA, SA, SA	SA (unbalanced 46, XX, der(10)t(10 ;15)(q26.1;q22.1)pat), SA (46,XX)
46, XY, t(7;8)(p11;p23)	SA, SA	Success (balanced 46, XY, t(7;8)(p11;p23)pat)
46, XY, t(4q;7q)	SA, SA	SA, SA, **GT (unbalanced 46, XY, der(4)t(4q;7q)pat),** SA, SA
46, XY, t(1;4)(q32.3;q31.3)	SA, SA, SA	SA (unbalanced 46, XY, der(1)t(1;4)(q32.3;q31.3)pat)
46, XY, t(2;7)(q31;q31.3)	SA, SA	SA (46,XY), Term, SA (47, XX, +22)
46, XY, t(8;13)(q22;q21)	SA, SA, SA, SA, SA	SA (47, XX, +trisomy)

Table 1 *(Continued)*

Carrier Status	Prior Pregnancies	Subsequent Pregnancies
46, XY, t(14;17)(q32.3;q21.1)	SA, SA	Term (balanced 46, XY, t(14;17)(q32.3;q21.1)pat)
46, XY, t(7;21)(q21.2;q11.2)	SA, SA, SA	Term (46, XY)
46, XY, t(8;15)(11.2;q25)	SA, SA, SA	SA (unbalanced 46, XY, der(8)t(8;15)(p11.2;q25)pat)
46, XY, t(3;4)(q12;q10)	SA, SA	Term
46, XY, t(3;10)(q23;q24)	SA, SA, SA	SA (unbalanced 46, XY, der(10)t(3;10)(q23;q24)pat), Term
46, XY, t(2;11)(q35;q14)	SA, SA, SA	SA (unbalanced 46, XY, der(11)t(2;11)(q35;q14)pat), SA (balanced 48, XY, t(2;11)(q35;q14)pat, +13, +16), SA (46, XX), **Term**
46, XY, t(6;7)(q16.2;q21.2)	SA, SA	Term
46, XY, t(12;13)(q21.3;q21.2)	SA, SA	Term (balanced 46, XX,inv(9)(p11q13)mat, t(12;13) (q21.3;q21.2)pat)
Jobanputra et al, 2005[17]		
46, XX, t(11;22)(q23;q11.2)	SA, SA, SA, SA, SA, SA, SA, SA, Term (balanced 46, XX, t(11;22)(q23;q11.2) Order not stated	SA (unbalanced 46, XY, +2,der(11)t(11;22)(q23;q11.2)mat, -22[4]/45, XY, der(11)t(11;22)(q23;q11.2)mat, -22[4]), Term (46, XX)
Stephenson and Sierra, 2006[7]		
46,XX, t(7;10)(p21;p13)	Term, ET (46, XY), SA, SA	Term (balanced 46, XY, t(7;10)(p21;p13)mat)
46,XX, t(4;6)(q35.2;q12)	SA, SA, SA	Term, SA (unbalanced 46, XY, der(4)t(4;6)(q35.2;q12) mat), Term
46,XX, t(2;6)(q33;q23)	Term, SA, SA, SA	Term
46,XX, t(2;4)(q36.3;q13.3)	SA, SA, Term, SA, SA	Preterm (balanced 46, XX, t(2;4)(q36.3;q13.3)mat)
46,XX, t(4;9)(q35;q31)	SA, SA (balanced 47, XX, t(4;9)(q35;q31)mat, +16), SA (balanced 46, XX, t(4;9)(q35;q31)mat)	Term (balanced 46, XX, t(4;9)(q35;q31)mat)
46, XX, t(1;6)(q42.1;q24.2)	SA, SA, SA	SA, Term (46, XX), SA (unbalanced 46, XY, der(1)t(1;6)(q42.1;q24.2)mat), Term
46, XX, t(8;12)(q22;q22)	SA, SA, SA, SA	SA, Term, SA (unbalanced 46, XY, -8, +der(12)t(8;12)(q22;q22)mat), SA (balanced 47, XX, t(8;12)(q22;q22)mat, +13)
46, XX, t(7;10)(q31.2;q23.2)	SA, SA, SA	Term (46, XY)
46, XX, t(2;12)(q13;q24.31)	SA, SA, SA, SA	Term
46, XX, t(3;19)(q25.1;q13.3)	ET, SA, SA	SA (unbalanced 47, XX, +der(19)t(13;19)(q22;q13)mat)
46, XY, t(5;12)(p15.1;p12.2)	SA, SA, SA	Term
46, XY, t(6;17)(q21;q24.2)	ET, SA, SA, SA (46, XX), SA	SA (47, XY, +13), SA, Term
46, XY, t(8;10)(p21.3;q24.3)	SA, SA (46, XX), SA	Term (46, XY)
46, XY, t(5;9)(q23.2;q22.3)	Term, SA, SA, SA	Term, Term
46, XY, t(8;18)(q11.2;q21.3)	SA, SA (69, XXY), SA, SA (unbalanced 46, XY, der(18)t(8;18)(q11.2;q21.3)pat)	Term
46, XY, t(7;13)(p13;q21.2)	SA, SA, SA, SA (unbalanced 46, XX, der(7)t(7;13)(p13;q21.2)pat)	SA (unbalanced 46, XX, der(13)t(7;13)(p13;q21.2)pat)
46, XY, t(6;13)(q10;q10)	SA, Term, SA, SA (unbalanced 47, XY, +6, der(6;13)(q10;q10)pat +16), SA (unbalanced 46, XY, +der(6;13)(q10;q10)pat, der(13;14)(q10;q10))	Term (balanced 46, XX, t(6;13)(q10;q10)pat)
46, XY, t(5;14)(q11.2;q32.1)	Term, SA, SA, SA	SA, SA, Term
46, XY, t(5;7)(p13;p15)	Term, Term, SA, SA, SA, SA (46,XY), SA	Term
46, XY, t(1;6)(p36.1;p22.1)	Term, SA, SA, SA (46, XY)	SA (46,XX), Term
Sugiura-Ogasawara et al, 2008[4]		