上でいつでも入手できることである（IDとパスワードで保護）。

またレーダーチャートにより自施設の位置の評価を行う機能を設けている。好成績を外周に配置しているので，自施設の優れている項目と低いランクの項目を一目で認識することができる（**図4**）。

B. 介入と改善②

「多変量解析によってアウトカムに関与する有意の臨床要因を探る」

大規模データベースが優れている点のひとつは，極低出生体重児のアウトカムに関与する周産期因子を多変量解析によって解析できることである。

表2は，ある施設のデータを取り上げ，コックス多変量解析により，全国のデータと比較して，死亡危険度（リスク人日比）をアウトカムとして，個々の施設の診療の安全性と質向上への手がかりを探ったものである（森，楠田 2010）。この施設の全国と比較した死亡危険度0.75は，児の重症度による交絡因子を調整すると0.51（p＝0.02）に改善する。つまり優秀な施設であるといえる。

表3に某NICUについて，死亡に関与する臨床因子の死亡危険度への影響を解析した結果を示す。例として，母体ステロイド投与有無について当該施設による交絡因子を調整した後の死亡危険度は0.51から0.56に9.8%増加する。この施設では母体ステロイドが積極的に実施された結果，死亡危険度は下げる方向に働いていることが，その働きの大きさも含めて説明されている。すべての有意な因子で調整後のハザード比は0.98［95% CI 0.56-1.72］，p＝0.93であり，この施設が全国平均よりも優秀な理由の多くはこれら因子で説明できる。

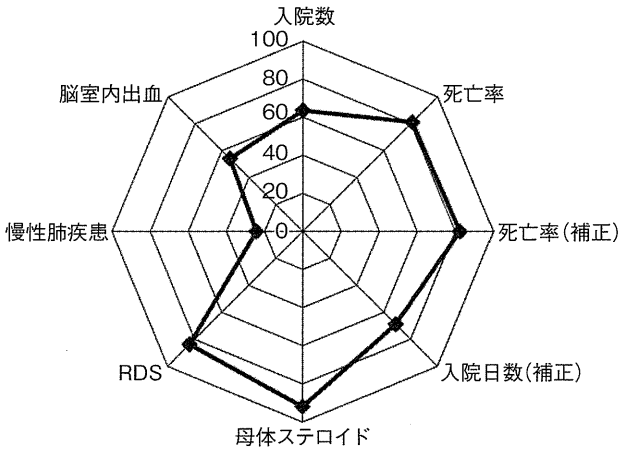

図4　レーダーチャートによる自施設の位置の評価
好成績を外周に配置

表2　某NICUを全国のデータと比較した死亡危険度（コックス多変量解析）

交絡因子の調整	死亡危険度	95%信頼区間	P値
調整前	0.75	［0.47～1.22］	p＝0.25
調整後	0.51	［0.29～0.89］	p＝0.02

（森，楠田　2010）

表3　某NICUの診療評価表。各因子による個の施設の死亡危険度への影響の解析

各交絡因子	当該因子による交絡を調整後の死亡危険度	0.51からの変化
母体steroid	0.56	9.8%
アプガー5<7	0.56	9.8%
酸素	0.50	2.0%
挿管	0.50	2.0%
RDS	0.50	2.0%
Air leak	0.52	2.0%
肺出血	0.49	3.9%
PPHN	0.52	2.0%

各交絡因子	当該因子による交絡を調整後の死亡危険度	0.51からの変化
PDA	0.50	2.0%
インダシン	0.50	2.0%
痙攣	0.55	7.8%
IVH	0.43	15.7%
PVL	0.52	2.0%
敗血症	0.55	7.8%
中心静脈栄養	0.67	31.3%
NEC	0.50	2.0%
消化管穿孔	0.50	2.0%

（森，楠田　2010）

C. 介入と改善③

「発達予後がアウトカムの本命。そのためにはフォローアップ体制の構築が必要」。「フォローの結果が出たら，臨床要因との相関を解析できる」

新生児集中治療におけるアウトカムの本命は，子どもの発育・発達予後である。そのためにはフォローアップ体制の構築が必要であるが，NICUの普及とは裏腹にわが国ではほとんど手つかずの状態であった。1994年に「極低出生体重児のフォローアップを考える会」(1998年からハイリスク児フォローアップ研究会に改組）が発足して，そこで乳幼児期の検診プロトコールがつくられ，全国的に同じ内容のフォローアップをする体制の構築が始まった。2010年には総合周産期母子医療センターの7割で心理士による発達評価が実施可能となっている。諸外国に遅れていたが，実はレベルⅢのNICUの大部分が，統一プロトコールを用いて全入院極低出生体重児をフォローアップするような体制は諸外国にも例をみないユニークなものであり，今後日本の強みとなり得る貴重な財産である。一方ではその業務負担は大きく，NICU診療で精一杯の現場では，フォローアップにまで十分な時間を割けないでいるのが現状である。

河野らは極低出生体重児のフォローアップデータベース（N＝3104）を用いて，予後に影響する要因の解析を行っており，CP合併する臨床因子について，消化管穿孔，脳室内出血3，4度，嚢胞性PVL等が有意の危険因子であるとまとめている（**表4**）。

米本，河野，藤村らは同じデータベースで27，28週児を1とした時の下位週児の脳性まひの危険率（オッズ比），及びDQ＜70（3歳）の危険率（オッズ比）を検討した。その結果，**図5**のように，CPの頻度は在胎期間による有意差がなく，一方発達遅延（DQ＜70）の頻度は週が小さくなるほど多いことを明らかにした。こうした研究は急性期患者データベースとフォローアップ結果データベースの構築があって初めて可能になるものである。

D. 介入と改善④

「新生児（周産期）医療提供体制の改革」

極低出生体重児の施設別死亡率は，NICUのレベル（つまりストラクチャー評価）と入院患者数に相関することがいくつかの国・地域で示されている[8]。規模が大きいこと自体がアウトカムを改善する。

周産期母子医療センターネットワークにおいてもそ

表4　CP合併の影響要因の解析

左欄の要因を調整した後，右欄の要因について脳性まひ発症との相関を解析すると，消化管穿孔，脳室内出血3，4度，嚢胞性PVL，晩期循環不全AOPが有意の危険因子(*)である。

調整要因	CP		
	OR	95% C.I.	
maternal age, per 1 year	0.94 *	0.90	0.99
gender, male	0.91	0.55	1.50
plurality, multiple	0.96	0.55	1.66
BW, per 250g	1.24	0.92	1.66
BW ＜10 percentile	0.56	0.28	1.14
antenatal steroid	1.56	0.94	2.58
caesarian section	0.91	0.51	1.62
outborn	1.24	0.58	2.62
Apgar score（1 min）＜4	1.45	0.84	2.53
RDS	1.45	0.59	3.55
symptomatic PDA	0.78	0.20	3.10
sepsis	1.27	0.57	2.84
gastrointestinal perforation	4.91 *	1.39	17.30
neonatal seizure	2.16	0.68	6.83
IVH grade 3 or 4	5.27 *	2.31	12.01
cystic PVL	27.26 *	12.39	59.96
CLD at 36 wks	1.14	0.62	2.12
intubation in DR	1.63	0.80	3.35
MV ≥ 1 day	0.75	0.28	2.04
S-TA	1.46	0.55	3.88
IND for PDA	1.51	0.38	6.07
PNS for CLD	1.22	0.59	2.56
AOP	2.62 *	1.17	5.90
treatment for ROP	1.04	0.59	1.86

周産期母子医療センターネットワーク（河野　2010）

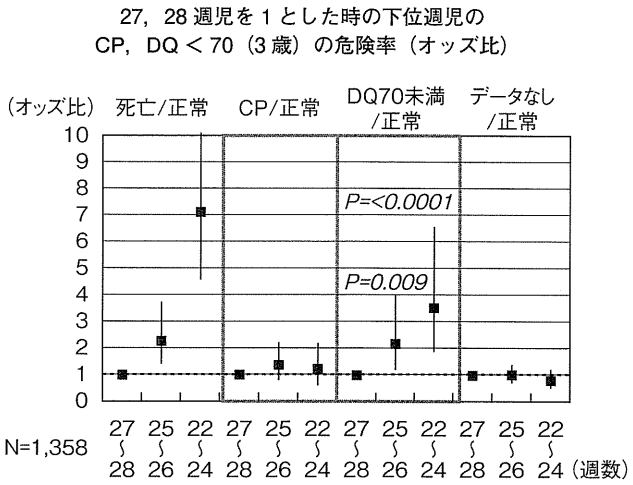

図5　27，28週児を1とした時の下位週児の CP，DQ<70（3歳）の危険率（オッズ比）。
CPの頻度は有意差がなく，DQ<70の頻度は週が小さくなるほど多い。
周産期母子医療センターネットワーク（米本，河野，藤村　2010）

表5　ハイリスク新生児医療の戦略

《為すべき事》
• ハイリスク新生児を基幹的NICUへ集約する
• 個々のNICUの治療成績を向上させる
《その基礎データ》
• NICUへの集約率をモニターする
• NICU退院児のアウトカムをモニターする
《医療機関ネットワークと行政は》
• NICU医療機関の配置計画と整備
• 新生児医療の地域ネットワークとベンチマーク

うした検討を行ってきた。**図6**はNICUの医師数と死亡率に相関が認められるという結果を示したものである。これからの新生児（周産期）医療提供体制の改革にデータベースは活用できると考えられる。

以上の結果から，ハイリスク新生児医療の戦略は**表5**のようにまとめられる。

結　　語

総合周産期母子医療センターネットワーク研究班における検討から，個別NICUの持続的改善モデルがひとつの成果として提案できる。

先ず患者データベースを構築してアウトカムと臨床因子の関係を解析し，その所見を用いて，テーラーメイドでストラクチャーとプロセスを改善する。それによってより良いアウトカムが得られたかどうかは，次年度以降の患者データベースで検証できる。その循環運動はNICU改善プロジェクトと名付けてよいものであろう（**図7**）。

これからの日本の新生児集中治療は，検証と介入に

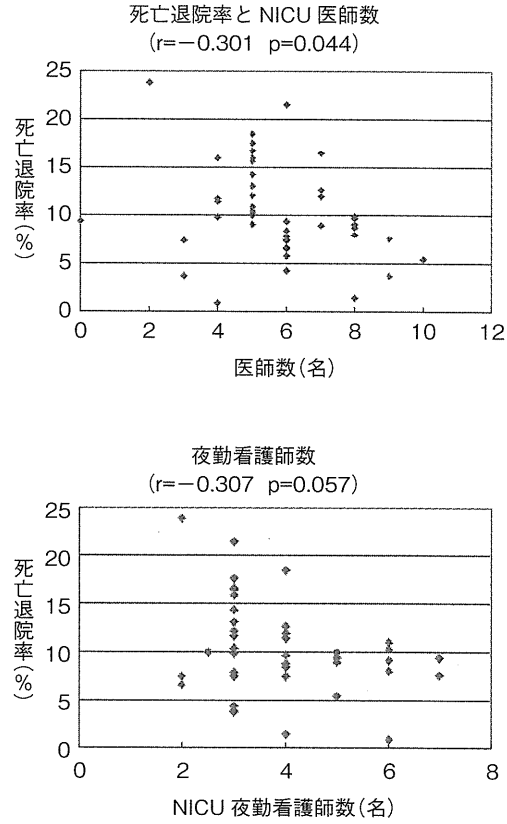

図6　NICUの医師数，夜勤看護師数と死亡率
周産期母子医療センターネットワーク（松浪，藤村　2008）

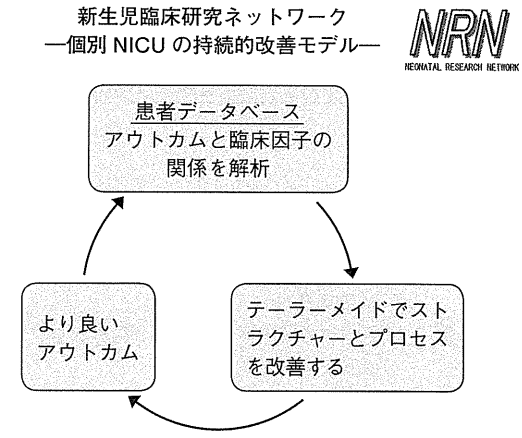

図7　NICU改善プロジェクト—新生児臨床研究ネットワーク

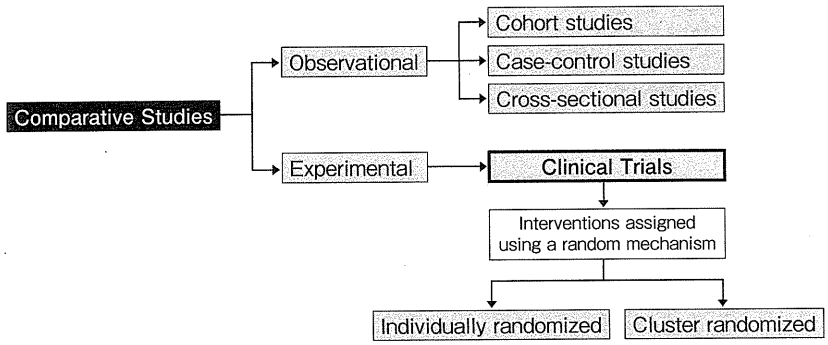

図8　臨床試験の施設別介入 Cluster randomized clinical trails

(Daniel Wojdyla, WHO Special Programme of Research, Development and Research Training in Human Reproduction, WHO, 2005)

よってさらに良い結果を目指すことが期待できる。今後の課題は「良い結果」としてどういう指標を取り上げるかということであろう。それは新生児医療が何を目指すかということでもあり，患者や社会を含めて新生児医療に関係するすべての人々によって合意されていることが望ましい。

さらにこうした改善プロジェクトの有効性を実証してゆくことが必要である。その方法のひとつとして，Cluster Randomized Clinical Trial を多施設の NICU で実施する計画が，厚生労働省科学研究の一課題として始まっている。医療の質を改善してゆく着実な動きのひとつとして確立してゆくことが期待される。

この発表に寄与された本研究の共同研究者にお礼申し上げます。

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文　献

1) 周産期医療の確保について．平成22年1月26日　都道府県知事宛て　厚生労働省医政局長
http://wwwhourei.mhlw.go.jp/hourei/doc/tsuchi/T100128G0010.pdf
2) 周産期医療センターの評価について．平成22年4月20日　都道府県母子保健主管部宛て　厚生労働省医政局指導課長
http://wwwhourei.mhlw.go.jp/cgi-bin/t_document.cgi?MODE=tsuchi & DMODE=CONTENTS & SMODE=NORMAL & KEYWORD= & EFSNO=998 & PAGE=1 & FILE= & POS=0
3) 新生児臨床研究ネットワーク　http://nrn.shiga-med.ac.jp/
4) 周産期母子医療センターネットワークデータベース解析報告
http://plaza.umin.ac.jp/nrndata/
5) 厚生労働科学研究成果データベース
http://mhlw-grants.niph.go.jp/
6) American Academy of Pediatrics. Guidelines for Perinatal Care (sixth edition). 2007 Washington, DC
7) British Association of Perinatal Medicine. Service Standards for Hospitals Providing Neonatal Care (3rd edition), 2010.
8) Phibbs S, Baker LC, Caughey AB, et al. Level and Volume of Neonatal Intensive Care and Mortality in Very-Low-Birth-Weight Infants. N Engl J Med 2007；356：2165-2175.

脳と発達　2011；43：206―210

特集　第52回日本小児神経学会総会
シンポジウム1：周産期脳障害と向き合うために―分野を超えた専門知識の相互リンクがもたらすもの

産婦人科医からみた周産期脳障害

池田智明

要旨　脳性麻痺の中で，分娩時に低酸素症が原因で発生する例は，全体の約20%であることを臨床研究で明らかにした．それ以外の原因と考えられる脳性麻痺の約75%が，分娩時に正常でない胎児心拍数（FHR）パターンが認められたことは，感染症や先天異常といった低酸素以外の異常を妊娠および分娩中に診断することが，予防や原因分析の観点からも重要である．動物実験から，asphyxia中は血圧のみが脳障害の予測因子であり，asphyxia後の様々なパラメータを観察することが予後予測のために重要であることが示された．分娩時asphyxiaの場合，新生児の観察，記録が重要であることを示した．

見出し語　周産期脳障害，脳性麻痺，胎児心拍数モニタリング，asphyxia，低酸素症

はじめに

平成21年（2009年）から，日本医療機能評価機構による産科医療補償制度がスタートした．この目的は，①分娩に関連して発症した脳性麻痺児およびその家族の経済負担補償と，②脳性麻痺発症の原因分析とその予防に資する情報提供をはかることである．平成23年現在，100例以上が認定され，20例以上の原因分析が終了している．目的が達成されるか否かを，今後見守っていく必要があろうが，産婦人科医を中心とした周産期脳障害に対する世界にも類をみないプロジェクトが開始されたことは間違いない．本稿では，産婦人科医からみた周産期脳障害について述べていく．

1．脳障害の発症時期としての「分娩時」と，発症原因としての「低酸素症」

胎児asphyxiaと小児脳障害について，最初に記載したのは，英国の整形外科医John Little（1810～1894）であった．彼は1861年，「異常分娩の影響」と題し，脳性麻痺に関する論文を産科学会で発表した．新生児仮死の他に，難産と早産が脳性麻痺の発生に関与することを63例の具体的な病歴と，新生児死亡例の剖検所見から示した[1]．異常分娩と新生期からの異常所見を，数年後の異常神経症状と関連づけ，その予防法と治療法を示したことは，画期的なことであった．しかし，障害児の発生時期が「分娩時」であるという彼の意見は，その後，医療のみでなく，一般的通念として長年にわたって信じられることとなる．

一方，「低酸素症」と胎児は，古くからのテーマであり，周産期学はこの問題とともに歩んできたといっても過言ではない．低酸素症が進行すると胎児は様々な代償反応を示し，さらに進行すると代償不全に陥り，脳をはじめとする臓器障害が発生し，さらに進行すると死に至るという考えは，“continuum of reproductive casualty”と呼ばれ，信じられてきた[2]．プエルトリコにおける，Myersらのアカゲザルを使った一連の動物実験も，この説を支持するものであった[3]．

したがって，分娩時における低酸素症を防ぐことができれば，脳性麻痺を始めとする周産期脳障害のほとんどが予防できると考えられたのも，ごく自然のことである．

2．「分娩時」かつ「低酸素症」による脳障害の発生の因果関係を示すためのガイドラインと周産期脳障害の実態

分娩時のasphyxiaが脳性麻痺の原因であることをいうために，1998年にオーストラリア・ニュージーランド周産期学会から出された基準がある（表1，2）[4]．これは，分娩中に急性低酸素症が発生したことを示す必須3基準項目，補助5基準項目，計8基準項目に分けて示している．さらに，この別項として，分娩中の急性低酸素以外の原因を示唆する13項目を設けていることが特筆すべき点である．子宮内感染症や先天異常などの非asphyxia性脳障害の原因を，出生前に積極的に診断することの重要性を謳ったものである．

この基準にしたがって，われわれは日本におけるフィールド研究を行った．年間約1万例の出生のある宮崎県において，1998～2002年にわたる5年間に109例を神経予後不良例として登録し，検討した[5]．1,000出生当たり2.0例の発生率であった．その原因別の内訳として，低酸素・虚血が主原因と考えられた例は，全体の19%であり，先天異常の25%に次い

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表1 急性の分娩時低酸素症が脳性麻痺の原因であることを示唆する基準

・必須基準
1．代謝性アシドーシス（pH<7.00，BD>=12 mmol/L）
2．新生児脳症（けいれん，意識障害など）妊娠34週以上
3．脳性麻痺（痙性四肢麻痺 or ジスキネジア型）
・分娩中発生を示唆するが，一つ一つでは非特異的基準
4．陣痛発来直前—分娩中に発生した前兆的イベント
5．胎児心拍数パターンの悪化
6．5分後 Apgar 指数 0-6 点
7．他臓器障害
8．急性脳障害の画像所見（浮腫像など）

オーストリア・ニュージーランド周産期学会の基準[4]

表2 分娩中の急性低酸素症以外の，脳性麻痺の原因を示唆する基準

1．pH>=7.0 and/or base deficit<12 mmol/L
2．大奇形，多発奇形，代謝異常
3．中枢神経または全身的な感染
4．出生早期の画像所見異常（脳室拡大，孔脳症など）
5．IUGR（intrauterine growth retardation）
6．分娩開始からの FHR 基線細変動の減少
7．出生時の小頭症（頭囲<=3%）
8．出生前の広範囲な胎盤早期剝離（慢性）
9．著明な絨毛膜羊膜炎
10．児の先天性凝固障害
11．出生前の他の脳性麻痺のリスクファクター（多胎など）
12．出生後の脳性麻痺のリスクファクター（呼吸疾患）
13．脳性麻痺の同胞

(MacLennan, BMJ, 1999[4])
FHR：胎児心拍数

表3 分娩時低酸素・虚血群（9例）の原因疾患

1．胎盤早期剝離
2．臍帯因子
3．前期破水（28h）子宮内感染，臍帯因子
4．臍帯因子，Vacuum 5回
5．臍帯因子，Vacuum 4回
6．過強陣痛
7．胎便吸引症候群（MAS）
8．双胎第2子骨盤位経膣
9．前置胎盤を誘導，出血

分娩時低酸素群11例の内訳を示す．脳障害となった9例は，早剝，臍帯因子，前期破水（28時間）・子宮内感染を合併した臍帯因子，全前置胎盤を助産院で誘導し，大出血が起こった例，過強陣痛，臍帯因子が原因と考えられVacuum 5回，MAS，双胎第2子骨盤位分娩が横位となってしまったもの，臍帯因子・Vacuum 4回．フォローアップ中に障害がなくなった2例は，過強陣痛，MASであった．

で第2位であった．未熟性（17%），脳室周囲白質軟化症（ただし，妊娠26週以上に限る）（16%），胎児発育不全（IUGR，ただし，低酸素・虚血や先天異常を伴わない例）（11%），先天性感染症（すべて先天性サイトメガロ感染症）（5%）と続いた．その他または不明は7%であった．

3. 分娩時の低酸素・虚血による脳性麻痺と，それ以外の脳性麻痺の胎児心拍数パターンの特徴

5年間109例の神経予後不良症例の中で，出生週数が34週以上の38例を選び，オーストラリア・ニュージーランド周産期学会から出された基準によって，分娩時低酸素・虚血群（分娩時低酸素群）と，それ以外の群（非低酸素群）に分類した．胎児心拍数（FHR）モニタリング判読可能な症例は，分娩時低酸素群は9例，非低酸素群は22例であった．分娩時低酸素群9例の原因疾患を表3に示す．FHRパターンは，NICHD[6]の基準によって検討した．その結果，9例すべて13分以上持続する徐脈を示した．臍帯動脈血はすべて7.0未満，base excessは−17 mEq/L未満と高度のアシドーシスを示した．帝王切開は9例中6例に行われた．

非低酸素群（22例）における，FHRパターンの異常を検討した．予定帝王切開を行った中枢神経奇形5例を除いた17例中，分娩時にreassuringであったものは4例のみであり，13例（76%）がnon-reassuring patternを示した．その内訳はdecreased baseline variability and/or late decelerationが6例，持続が5分間以内のprolonged decelerationが8例であった（ただし，1例が両所見を有した）．これらの症例は，FHRパターンから分娩時の低酸素症が脳障害の原因とみなされる可能性がある．したがって，中枢神経奇形，サイトメガロウイルス胎内感染症など，脳障害につながる異常を早期に診断し，記録することが，医学的のみでなく医事紛争を防止する観点からも望まれる．

4. ヒツジ胎仔を使った胎児 asphyxia の研究

臨床的検討によって，分娩時低酸素群において，重度除脈にアシドーシスが伴った場合に，脳障害が発生することが示された．このことから，このような状況を動物モデルで作成し，脳障害の関連因子を検討した．Near-termのヒツジ胎仔26頭を用い，臍帯にオクルーダーを装着した後，最低3日間待って実験を行った．オクルーダーを膨らますことによって，臍帯血流を部分的に遮断しasphyxiaを負荷した．胎仔動脈血のpHが6.9かつbase excessが−20 mmol/Lになるまでの約60分間，閉塞を続けた．その後，72時間の生理学的パラメータ（胎仔心拍数，胎仔呼吸様運動，脳波）と生化学的パラメータ（血液ガス，血糖，乳酸）の変化を観察した後に，脳，心，腎および肝を摘出し，組織学的に検討した．

アシドーシス状態を一定にしたにもかかわらず，脳障害の程度は軽症から重症までさまざまであった．脳障害の程度を，軽症（白質障害のみ），中等症（白質障害かつ軽度または中等度灰白質障害），および重症（白質，灰白質とも重度障害）の3段階に分類し，それぞれのパラメータとの関連性を検討した．

5. Asphyxia 中において脳障害程度と関連するパラメータ（血圧）

図1，2にasphyxia前後の胎仔心拍数と平均血圧の変化を軽症群，中等症群，重症群に分けて示した．胎仔心拍数の変化は3群間で有意な相違がなかったのに対し，asphyxia中における低血圧の程度が進み，低血圧の持続時間も長くなるにつ

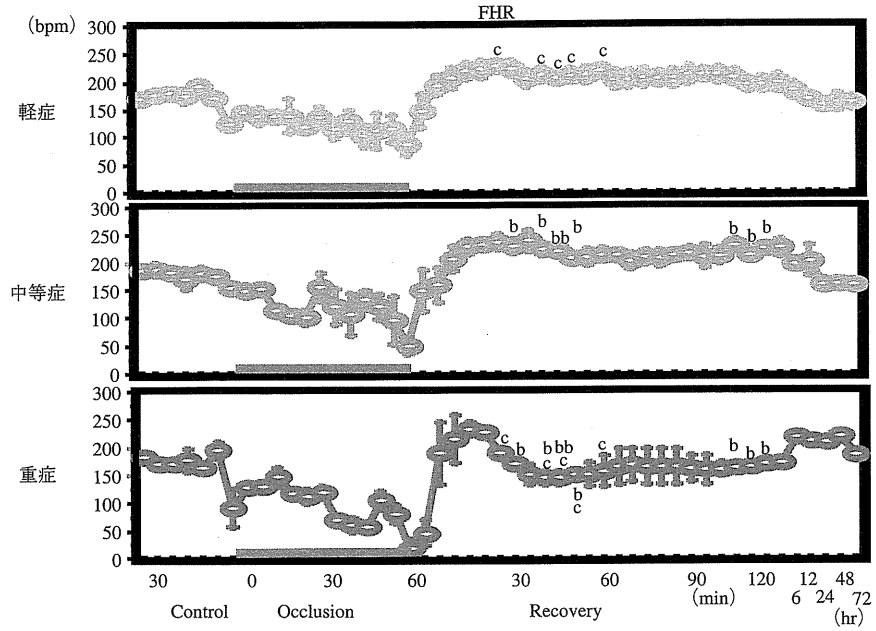

図1 Asphyxia 前後の胎児心拍数の変化

FHR の変化において，occlusion 中の徐脈も，3 群の間で統計学的有意差はなかった．

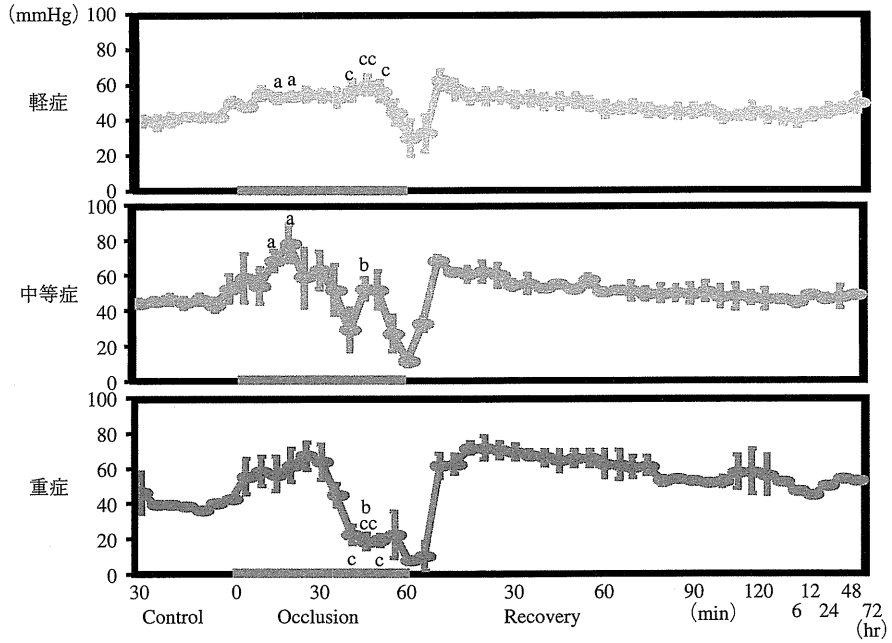

図2 Asphyxia 前後の平均血圧変化

Mean blood pressure は，軽症，中等症，重症となるにつれて，低血圧の程度が強くなった．
脳の重症度を横軸に，低血圧の持続時間と，徐脈の持続時間を縦軸に表した．低血圧を平均血圧 30，または 20 mmHg と定義しても，脳の重症度とに有意な相関があることがわかる．一方，徐脈時間は，100 bpm 以下，80 bpm 以下と定義しても相関はなく，どの障害度でも 80 bpm，約 8 分ぐらいを示した．

れて脳障害の程度が進んだ．本実験では脳血流量を同時に測定していないが，脳血流低下が低血圧に伴うことは Fujii らの実験が示すところである[7]．

臨床的に胎児血圧をモニターできない現在，asphyxia 中，胎児血圧以外の所見をもって正確な障害を予測することは困難であることがうかがえる．逆に，分娩時に胎児血圧を推定する方法があれば，脳障害の危険性をより正確に予測でき，さらに胎児 asphyxia の診断による帝王切開率を減少させるこ

表4 Asphyxia後における脳障害程度と関連するパラメータ

	Asphyxia中	Asphyxia後
血圧	低下するほど重症	一部に差があり
心拍数	差なし	一部に差があり
脳波（けいれん波）	差なし	中等症，重症であり
脳波二相性	差なし	重症で回復しない
FHR variability	差なし	3群で特有の変化
呼吸様運動	差なし	重症で回復しない
腎臓：尿細管壊死		中等症＜重症
肝臓，心臓		重症で障害

脳障害の程度において，asphyxia中に3群で違いがあったのは，血圧のみであった．Asphyxia後は，心拍数，脳波，FHR variability，呼吸様運動，腎臓，肝臓，心臓病理とも特有の変化を示した．

表5 新しい胎児心拍数波形分類

1	正常波形		Normal pattern
2	亜正常波形		Benign variant pattern
3	異常波形	軽度	Mild variant pattern
4	異常波形	中等度	Moderate variant pattern
5	異常波形	高度	Severe variant pattern

（日本産婦人科学会 2010[8]）

胎児心拍数波形を胎児のアシドーシスなどのリスクを推量する5段階に分類する．
胎児機能不全の診断は，波形［3～5］で行う．

表6 医療機関における胎児心拍数波形分類に基づく対応と処置

波形レベル	対応と処置	
	医師	助産師*
1	A：経過観察	A：経過観察
2	A：経過観察	B：連続監視，医師に報告する．
	又は	
	B：監視の強化，保存的処置の施行及び原因検索	
3	B：監視の強化，保存的処置の施行及び原因検索	B：連続監視，医師に報告する．
	又は	又は
	C：保存的処置の施行及び原因検索，急速遂娩の準備，新生児蘇生の準備	C：連続監視，医師の立ち会いを要請
4	C：保存的処置の施行及び原因検索，急速遂娩の準備，新生児蘇生の準備	C：連続監視，医師の立ち会いを要請
	又は	又は
	D：急速遂娩の実行	D：連続監視，医師の立ち会いを急ぎ要請，新生児蘇生の準備
5	D：急速遂娩の実行	D：連続監視，医師の立ち会いを急ぎ要請，新生児蘇生の準備

*ここでいう施設は，助産所を除く．

とが可能であると考えられる．

6. Asphyxia後における脳障害程度と関連するパラメータ

Asphyxiaの後では，心拍数，脳波所見，FHRパターン（基線細変動），呼吸様運動，腎臓，肝臓，心臓病理所見などが特有の変化を示した（表4）．臨床的に障害発生後のパラメータの観察が引き続く脳障害発生を予知する上で極めて重要であることが示された．前述のオーストラリア・ニュージーランドの基準においても，重症アシドーシス以外の3項目（新生児脳症，低Apgarスコア，多臓器障害）はいずれも，asphyxia後の所見である．新生児脳症は，けいれん，意識障害，筋緊張異常などが生後早期（定義では7日以内であるが，24時間以内が典型的である）に認められる徴候であり，分娩時asphyxiaが直接脳障害の原因と考えられるまで重症であったかどうかを後方視的に判定する場合，その有無は非常に重要である．新生児の詳細な観察と記載が日常臨床で今後，より徹底される必要がある．また，asphyxia性脳障害の診断はasphyxia中のFHRパターン，胎児血所見のみで確定することはできず，asphyxia後の生理的・生化学的パラメータをあわせて総合的に行われるべきである．産科医療補償制度における，原因分析においても，asphyxia後の所見を重要視し，情報を集めなければならないと考える．

7. 日本産科婦人科学会による分娩時胎児心拍数モニタリングガイドライン

FHRパターンの用語の標準化はなされた感があるが，胎児状態の推定や臨床的対応に関して，標準的なガイドラインの必要性が2000年代に求められるようになった．英国産婦人科学会ガイドライン（RCOG）が2001年に，カナダ産婦人科学会は2007年に，FHRパターン評価に加えて，臨床的対応ま

で踏み込んだガイドラインを発刊した．これは，FHRパターンを正常（normal），疑い（suspicious）または異型（atypical），異常（pathological または abnormal）の3段階に分けるものである（3 tier system）．2007年にParerと筆者は，FHRパターンを5段階（green，blue，yellow，orange，red）に分類し，それぞれに対して臨床的対応のサンプルを提唱した（5 tier system）（X）．これらを受けて，米国産婦人科学会（ACOG）も，米国周産期学会（SMFM），およびNICHDの3団体合同の再評価ワークショップを2008年4月に，胎児心拍数モニタリングワークショップ会議で，FHRパターンが，カテゴリーⅠ（正常：normal），カテゴリーⅡ（未決定：indeterminate），およびカテゴリーⅢ（異常：abnormal）と3つに分類することが決まった．

日本産科婦人科学会周産期委員会（岡井　崇委員長）も，2010年に「胎児心拍数波形の判読に基づく分娩時胎児管理の指針」を発表した[8]．この指針は，分娩中のFHRパターンに基づき，胎児警戒レベルを5つに分類し（表5，6），現在の医学的知識から妥当とみなされる4段階の対応と処置を示した．しかし，いずれのガイドラインも，帝王切開などの器械分娩率を増加させることなく新生児アシドーシスの減少につながるという有効性を示すことができていない．したがって，今後はこの有効性の検証がガイドラインの最大の課題である．

ま　と　め

周産期脳障害は，宮崎県をフィールドとする臨床研究によって，「分娩時」と「低酸素」以外の原因によって，約80%の症例が発症していることが推定された．この中の約75%に分娩時の正常でないFHRパターンが認められたことは，感染症や先天異常といった低酸素以外の異常を妊娠および分娩中に診断することが，予防の面からも，原因分析の観点からも重要であることの証明になった．この低酸素以外の要因をスクリーニングする上でも，オーストラリア・ニュージーランド周産期学会の基準が有用である．さらに，動物実験から，asphyxia中は血圧のみが脳障害の予測因子であり，予測因子はasphyxia後の変化が重要であることが示された．分娩時asphyxiaの場合，新生児の観察，記録が重要であることが動物実験によっても示された．

文　献

1) Little W. On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum on the mental and physical condition of the child, especially in relation to deformities. *Trans Obstet Soc London* 1861;**3**:293.
2) Lillienfeld AM, Parkhurst E. A study of the association of factors of pregnancy and parturition with the development of cerebral palsy.;a preliminary report. *Am J Hyg* 1951;**53**:262-82.
3) Myers RE. Experimental brain damage in the newborn monkey. *J Neuropahthol Exp Neurol* 1967;**26**:172.
4) MacLennan AA. A template for defining a causal relation between acute intrapartum events and cerebral palsy:international consensus statement. *BMJ* 1999;**319**:1054-9.
5) 池田智明，池ノ上克，鮫島　浩，ら．Asphyxia性脳障害の診断に関する臨床的および基礎的研究．日新生児会誌 2003;**39**:724-32.
6) Electronic fetal heart rate monitoring:research guidelines for interpretation. The National Institute of Child Health and Human Development Research Planning Workshop. *J Obstet Gynecol Neonatal Nurs* 1997;**26**:635-40.
7) Fujii EY, Takahashi N, Kodama Y, Roman C, Ferriero DM, Parer JT. Hemodynamic changes during complete umbilical cord occlusion in fetal sheep related to hippocampal neuronal damage. *Am J Obstet Gynecol* 2003;**188**:413-8.
8) 岡井　崇，池田智明，瓦林達比古，ら．委員会提案—胎児心拍数波形の分類に基づく分娩時胎児管理の指針（2010年版）—．日産婦会誌 2010;**62**:2068-73.

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ORIGINAL ARTICLE
Aortic Disease

Pregnancy-Associated Aortic Dilatation or Dissection in Japanese Women With Marfan Syndrome

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Background: Aortic dilatation and dissection are severe complications of pregnancy that may cause maternal death. The purpose of the present study was to investigate risk factors for aortic dilatation or dissection in pregnant Japanese women with Marfan syndrome.

Methods and Results: A total of 28 patients with Marfan syndrome were investigated retrospectively during pregnancy and after delivery at 1 institution. These patients were divided into 2 groups: those who experienced aortic dilatation or dissection (group D, n=11) and those who did not (group ND, n=17). In group D, aortic dilatation or dissection occurred in 7 cases during pregnancy (2 in the 2nd trimester, 5 in the 3rd trimester) and 4 cases after birth. The 2 cases in the 2nd trimester involved aortic dilatation >60 mm and those patients underwent hemiarch replacement and a David operation, respectively. Delivery by cesarean section (64% vs. 18%, P<0.05), sinus of Valsalva ≥40 mm (86% vs. 21%, P<0.05), aortic size index (size of sinus of Valsalva/body surface area) ≥25 mm/m^2 (7/7, 100% vs. 0/14, 0%, P<0.0001), and faster growth of the sinus of the Valsalva (median, [interquartile range]: 0.41 mm/month [0.23–0.66 mm/month] vs. 0.05 mm/month [–0.13 to 0.22 mm/month]; P<0.05) were significantly higher in group D than in group ND.

Conclusions: A large sinus of Valsalva, increased aortic size index, and rapid growth of the sinus of Valsalva are risk factors for aortic dilatation or dissection in pregnant Japanese women with Marfan syndrome. (*Circ J* 2011; **75:** 2545–2551)

Key Words: Aortic dissection; Aortic size index; Marfan syndrome; Pregnancy; Sinus of Valsalva

Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in the fibrillin-1 (FBN1) gene located on chromosome 15.[1] These mutations result in weakness of the supportive tissue of the body, and clinical characteristics include symptoms of the cardiovascular, skeletal, and ocular systems.[2,3] Cardiovascular complications are the main cause of morbidity and mortality in patients with Marfan syndrome.[4] Before the development of preventive surgical approaches to aortic diseases, the mean life expectancy for a patient with Marfan syndrome was <40 years, with aortic dissection, aortic rupture and cardiac failure being the predominant causes of death.[5] Beta-blocker therapy and elective surgical repair, however, have increased life expectancy to near normal values.[6]

Editorial p2532

Pregnancy is strongly associated with life-threatening problems in Marfan patients. The risk of aortic dilatation or dissection increases during and after pregnancy in patients with Marfan syndrome due to superimposition of the hyperdynamic and hypervolemic circulatory state of pregnancy on the preexisting weakness of the aortic media.[3] The rate of aortic dissection during pregnancy has been studied in previous reports. In 1981, Pyeritz reported no aortic complications during 105 pregnancies in 26 women affected by Marfan syndrome, based on phone interviews.[7] Rossiter et al prospectively followed 45 pregnancies in 21 women, and found 2 cases complicated by dissection;[8] Lipscomb et al reported 6 aortic events, including 4 aortic dissections, in 91 pregnancies in 36 women;[9] Lind and Wallenburg found 5 aortic dissections in 117 pregnancies;[10] and Pacini et al reported 7 aortic dissections in 160 pregnancies in 85 women.[11] Combining all these data gives a risk of 3.9% for aortic complication during pregnancy in women with Marfan syndrome who are not taking β-blockers.

The indicators of aortic risk in pregnancy are an aortic diam-

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Table 1. Patient Features vs. Presence of Aortic Dilatation or Dissection

	Group D (n=11)	Group ND (n=17)	P value
Maternal age (years)†	29.5±3.5	30.1±4.0	NS
Height (cm)†	167.3±4.5	165.3±4.2	NS
Weight (kg)†	65.3±4.5	64.5±3.9	NS
Nulli/Multiparous‡	8/3	12/5	NS
Gestation (weeks)†	36.2±3.2	37.0±2.8	NS
Birth weight (g)†	2747±705	2769±599	NS
Delivery mode‡			<0.005
Vaginal delivery	4	14	
Cesarean section	7	3	
BMI†	24.2±1.5	24.1±1.8	NS
DM‡	2	3	NS
Hypertension‡	2	3	NS
Smoking‡	2	3	NS

Data given as n or mean±SD. †Student's t-test; ‡chi-square test and Fisher's exact test. P<0.05, significant difference. D, aortic dilatation or dissection; ND, no aortic dilatation nor dissection; BMI, body mass index; DM, diabetes mellitus.

Table 2. Diagnostic Categories for Marfan Syndrome (Ghent Criteria[18])

Category	Group D (n=10)		Group ND (n=12)	
	Major	Minor	Major	Minor
Skeletal	10	3	11	2
Ocular	2*	1	8*	1
Cardiovascular	10*	3	7*	5
Pulmonary	–	3	–	2
Skin	–	0	–	1
Dura	2	–	5	–

Data were analyzed using chi-square test and Fisher's exact test.
*P<0.05.
Abbreviations see in Table 1.

eter ≥4.0 cm[7–10,12,13] and a steady increase in the aortic root dimension during pregnancy.[9,10,14] Meijboom et al reported that pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm.[15] Most previous reports on Marfan syndrome in pregnancy, however, have been from North America or Europe, and people in these areas have relatively large physiques, and patient physique was not standardized. Because normal aortic dimensions vary with age and body size,[16] the same aortic dimension represents a proportionally greater diameter in smaller individuals, and proper interpretation of the aortic dimension requires that age and body size are accounted for. Therefore the absolute aortic size cannot be directly used to evaluate risk in patients with a small physique,[17] such as Japanese women.

The risk factors for aortic complications in pregnant patients affected with Marfan syndrome have not been examined relative to body surface area. Therefore, to improve patient management, we studied 28 consecutive pregnant patients with Marfan syndrome in 1 institution to determine the factors that influence maternal aortic complications.

Methods

Patients

We retrospectively analyzed 28 consecutive pregnant patients with Marfan syndrome who were managed at the National Cerebral and Cardiovascular Center from 1991 to 2007. Diagnosis of Marfan syndrome was made based on the original Ghent criteria (1996).[18] Cases before 1996 were confirmed to fulfill these criteria. The initial assessment included an evaluation of personal history and detailed family history, and a clinical examination including ophthalmological tests and a transthoracic echocardiogram.[3] X-ray was used to detect protrusion acetabulae, and lumbar magnetic resonance imaging (MRI) was performed to detect dural ectasia.

We divided the patients into 2 groups: those with aortic dilatation or dissection (group D, n=11) during pregnancy or within 1 year after delivery and those without aortic dilatation or dissection (group ND, n=17). Aortic dilatation was defined as a diameter >60 mm at any part of the aorta.

Measurement of Aortic Diameter and Indication for Surgery

Measurement of the sinus of Valsalva was made on echocardiography in 2-D parasternal long-axis views at end-diastole using the leading edge to leading edge method.[16,19] MRI and computed tomography were not routinely used. The Japanese Circulation Society recommends an operation for patients with a sinus of Valsalva >5 cm (class IIa, level C) in all cases of Marfan syndrome.[20] Some surgeons also recommend an operation for patients with a sinus of Valsalva >4.5 cm.[21] At the National Cerebral and Cardiovascular Center, surgical intervention is indicated according to the aforementioned criteria and for patients with a family history of dissection or sudden death. In general, surgical intervention is indicated for a sinus of Valsalva >4.0 cm or in a case of steady aortic growth.[22,23] During pregnancy, surgical intervention is indicated if there is steady aortic growth or massive dissection. To standardize the measurement based on body size, we expressed the size of the sinus of Valsalva using the aortic size index (ASI), which is calculated as: ASI=aortic diameter (mm)/body surface area (m^2).[17]

Management During Pregnancy

Echocardiographic follow-up including aortic diameter measurement and Holter electrocardiogram was performed at least once in each trimester during pregnancy and within 4 weeks after delivery. When surgical intervention was indicated, the operation was performed after cesarean section in the case of a mature fetus. When the fetus was too immature to live independently, the operation was performed with the fetus in the uterus.

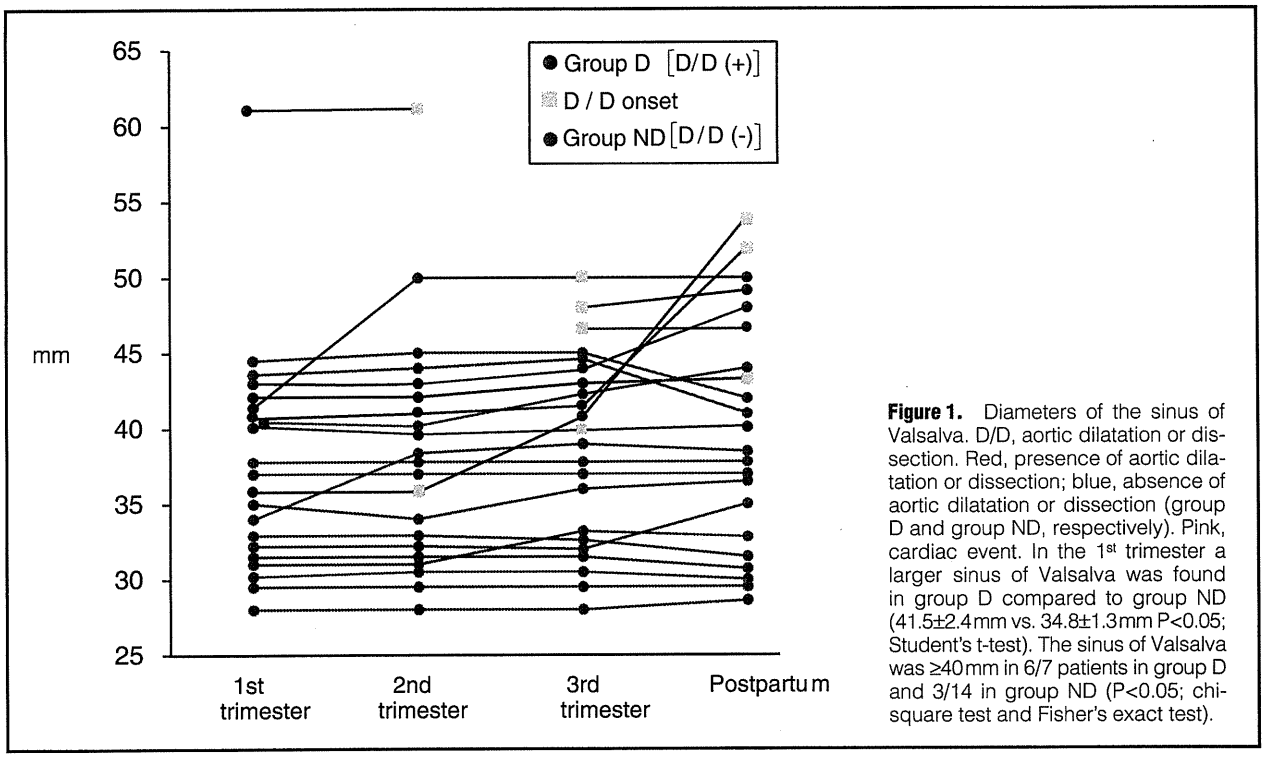

Figure 1. Diameters of the sinus of Valsalva. D/D, aortic dilatation or dissection. Red, presence of aortic dilatation or dissection; blue, absence of aortic dilatation or dissection (group D and group ND, respectively). Pink, cardiac event. In the 1st trimester a larger sinus of Valsalva was found in group D compared to group ND (41.5±2.4mm vs. 34.8±1.3mm P<0.05; Student's t-test). The sinus of Valsalva was ≥40mm in 6/7 patients in group D and 3/14 in group ND (P<0.05; chi-square test and Fisher's exact test).

Table 3. Echocardiographic Findings vs. Presence of Aortic Dilatation or Dissection

Item	Group D (n=11)	Group ND (n=17)	P value
Sinus of Valsalva (mm) in first trimester†	44.1±10.2	34.8±5.5	<0.005
Growth of aorta (mm/month)‡	0.41 (0.23–0.66)	0.05 (–0.13 to 0.22)	<0.005
Aortic valve regurgitation§			
None-Mild	5	15	<0.05
Moderate-Severe	6	2	
Mitral valve prolapse§	6	3	<0.05
LVDd†	45.8±7.1	44.8±6.8	NS
LVDs†	31.1±4.7	30.1±4.6	NS
%FS†	36.5±5.6	37.5±4.6	NS
RA cavity enlarged§	2	3	NS
RV cavity enlarged§	2	2	NS
PA dilatation (≥20mm)§	3	2	NS

Data given as mean±SD, n, or median (interquartile range).
†Student's t-test; ‡Wilcoxon test; §chi-square test and Fisher's exact test. P<0.05, significant difference.
LVDd, left ventricle end-diastolic dimension; LVDs, left ventricle end-systolic dimension; FS, fractional shortening; RA, right atrium; RV, right ventricle; PA, pulmonary artery. Other abbreviations see in Table 1.

Data Collection

Data were collected on family history (sudden death, aortic dilatation or dissection), maternal age, body height, body weight, parity, presence or absence of hypertension, diabetes mellitus, change in the diameter of the sinus of Valsalva during and after pregnancy, right and left ventricular function, aortic valve regurgitation, mitral valve prolapse, delivery mode (Cesarean section or vaginal delivery), time of delivery (gestational weeks), and birth weight.

Statistical Analysis

For continuous variables, Student's t-test was used for analysis of normally distributed data and the Wilcoxon test was used for data that were not normally distributed. A chi-squared test and a Fisher's exact test were used for comparing categorical variables between the 2 groups. All statistical analyses were performed using JMP 7 (SAS Institute, Cary, NC, USA). P<0.05 was considered statistically significant.

Results

Aortic Dilatation or Dissection Group

Eleven patients had aortic dilatation or dissection associated with pregnancy (in 7 this occurred during pregnancy and in 4 it occurred within 1 year after pregnancy). Two of the 7 antepartum cases involved aortic dilatation >60mm (maximum diameter of the aorta) in the 2nd trimester at 16 and 19 weeks of gestation, respectively. One patient underwent hemiarch

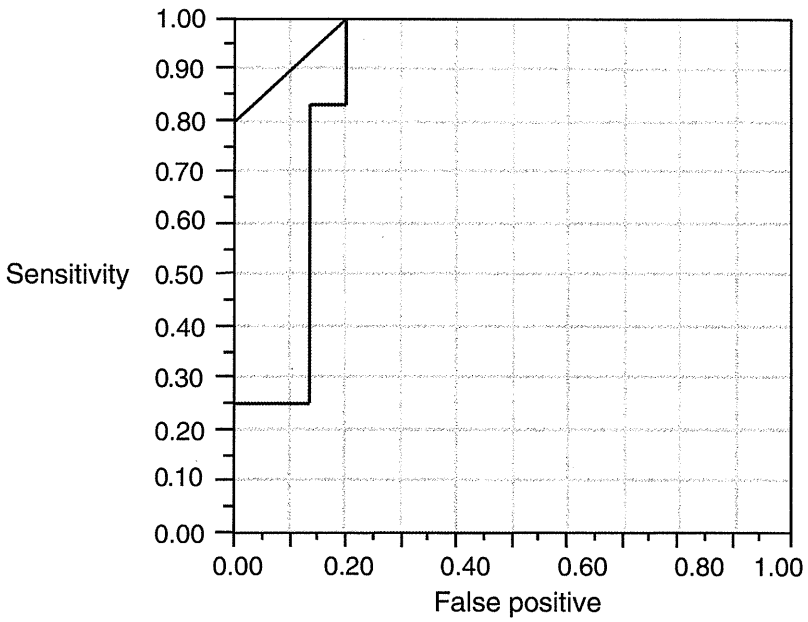

Figure 2. Receiver operating characteristic curve for the risk of dilatation or dissection based on the size of the sinus of Valsalva.

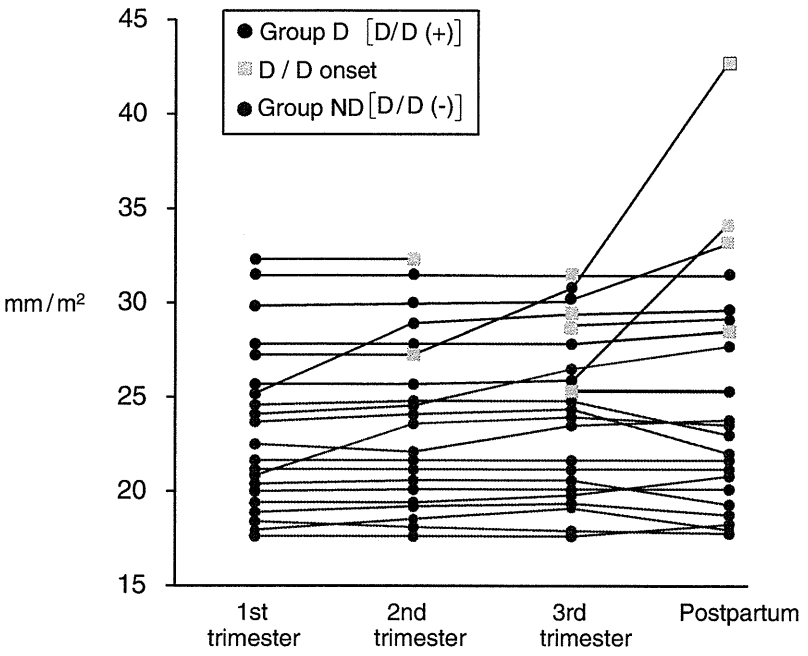

Figure 3. Sinus of Valsalva relative to body surface area (size of the sinus of Valsalva/body surface area: mm/m²). D/D, aortic dilatation or dissection. Red, presence of aortic dilatation or dissection; blue, absence of aortic dilatation or dissection (group D and group ND, respectively). In the 1st trimester the normalized size of the sinus of Valsalva was ≥25 mm/m² in 7/7 patients in group D and 0/14 in group ND (P<0.0001; chi-square test and Fisher's exact test).

replacement and the other underwent a David operation under cardiopulmonary bypass with the fetus in the uterus. The other 5 dissections during pregnancy occurred at 29, 33, 34, 35 and 39 weeks of gestation. Of these 5 patients, 3 underwent Bentall operations following cesarean section and 2 received conservative therapy after cesarean section. Dissection in the 4 postpartum cases occurred at 4 days, 8 months, 18 months, and 11 months after delivery, respectively. Of the 11 dilatation or dissection cases, 8 occurred in the ascending aorta, 1 in the descending aorta, and 2 in both locations.

Demographic Patient Data

The maternal age, week of delivery, and birth weight did not differ between the D and ND groups (**Table 1**). The incidence of cesarean section was higher in group D than in group ND (7/11, 63.6% vs. 3/17, 17.6%, P<0.05). This was attributed to performance of cesarean section due to occurrence of dilatation or dissection of the aorta during pregnancy. The number of patients meeting each diagnostic category for Marfan syndrome (Ghent criteria, 1996)[18] is given in **Table 2**. In group D, fewer patients met the major ocular criteria (2/10, 20% vs.

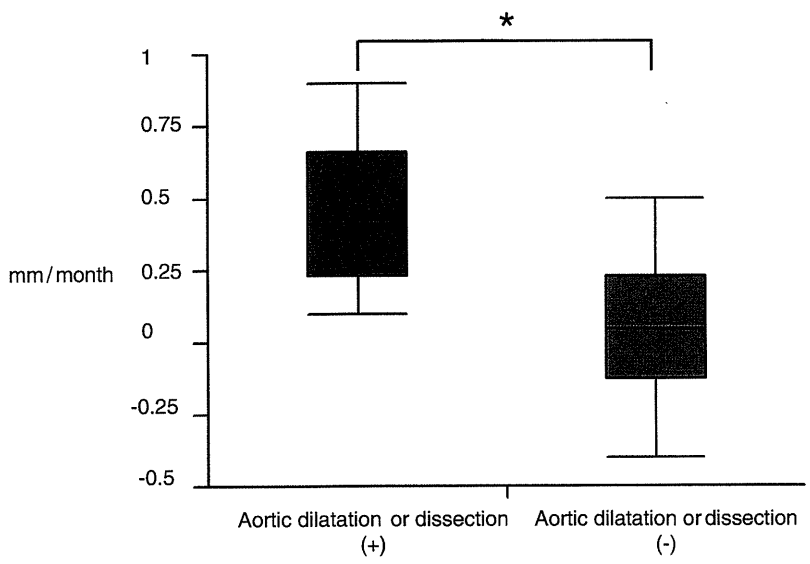

Figure 4. Rate of growth of the sinus of Valsalva. Significantly faster growth of the sinus of Valsalva was observed in group D (red) than in group ND (blue). The middle bar indicates the 50th percentile; box edges are the 25th and 75th percentiles; and outer bars are the 10th and 90th percentiles. Data were analyzed using Wilcoxon test. *P<0.05.

8/12, 67%, P<0.05) and more patients met the major cardiovascular criteria (10/10, 100% vs. 7/12, 58%, P<0.05). Gene analysis was performed in 11 of the 28 cases (40%) and a fibrillin-1 mutation was found more commonly in group D, although the difference was not significant (4/4, 100% vs. 4/7, 57%, P=0.06). A family history of sudden death or aortic dissection was more frequent in group D (7/11, 64% vs. 4/17, 24%, P<0.05).

Echocardiographic Patient Data

The sinus of Valsalva in the 1st trimester of pregnancy was significantly larger in group D than in group ND (mean [range]: 44.1 mm [36–61 mm] vs. 34.8 mm [28–45 mm], P<0.005; **Figure 1**; **Table 3**) and a sinus of Valsalva ≥40 mm in the 1st trimester was more frequent in group D (6/7, 86% vs. 3/14, 21%, P<0.05; **Figure 1**). On receiver operating characteristic (ROC) analysis of the relationship of the size of the sinus of Valsalva in the 1st trimester with aortic dilatation or dissection during pregnancy and after birth, the area under the curve (AUC) was 0.837 and the size of the sinus of the Valsalva that produced the best sensitivity (1–specificity) was 40 mm (**Figure 2**).

An ASI (diameter of the sinus of Valsalva/body surface area) ≥25 mm/m² was more frequent in group D than in group ND (7/7, 100% vs. 0/14, 0%; P<0.0001; **Figure 3**). On ROC analysis of the relationship of the ASI in the 1st trimester with aortic dilatation or dissection during pregnancy and after birth, the AUC was 0.985 and the size of the sinus of Valsalva that produced the best sensitivity (1–specificity) was 25 mm/m². In 1 case, aortic dissection occurred in a patient with a sinus of Valsalva of only 36 mm in the 1st trimester. Her ASI, however, was 27.3 mm/m² (36 mm/1.31 m²), which was the 5th largest in the study. This indicates that normalizing the sinus of Valsalva measurement with respect to body surface area is more appropriate for prediction of aortic dilatation or dissection, compared to the absolute diameter. Significantly faster growth of the sinus of Valsalva was also observed in group D (median [interquartile range]: 0.41 mm/month [0.23–0.66 mm/month] vs. 0.05 mm/month [–0.13 to 0.22 mm/month]; P<0.05; **Figure 4**).

The sizes of the right and left ventricles did not differ between the 2 groups (**Table 3**). In the 1st trimester of pregnancy, patients in group D had more frequent moderate to severe aortic valve regurgitation (6/11, 55% vs. 2/17, 12%; P<0.05) and mitral valve regurgitation (6/11, 55% vs. 3/17, 18%; P<0.05). These effects were already present before conception and may be 1 of the causes of dilatation or dissection.

Discussion

This is the first study to investigate the risk factors for pregnancy-associated dilatation or dissection in Japanese patients with Marfan syndrome. The risk factors that differed significantly between groups D and ND were mostly consistent with those found in previous studies.[7–10,14] These factors included a large sinus of Valsalva, rapid growth of the sinus of Valsalva during pregnancy, moderate to severe aortic valve or mitral valve regurgitation, and a family history of sudden death or aortic dissection.

We found that a large sinus of Valsalva (≥40 mm) at the start of pregnancy was a risk factor for dilatation or dissection during pregnancy and after birth. The present result differs from the findings of the relatively large prospective study by Meijboom et al, in which it was concluded that pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm,[15] and from Canadian guidelines that recommend that women with an aortic root diameter beyond 44 mm should be strongly discouraged from becoming pregnant.[24] Taking into account that Japanese women have a generally smaller physique than European and North American women, we recommend that the cut-off for Japanese patients for advice regarding avoidance of pregnancy should be a sinus of Valsalva diameter ≥40 mm, rather than ≥45 mm. In a case report on a patient who developed a massive retrograde type B aortic dissection 7 days after normal spontaneous vaginal delivery, Gandhi et al described the patient as "petite" (body surface area, 1.69 m²), but this is still larger than the average Japanese woman.[25]

We also suggest that normalizing the diameter of the sinus of Valsalva with regard to body surface area (diameter of the Valsalva/body surface area; mm/m²) may be more appropriate

for detection of high-risk cases at the start of pregnancy. The relative aortic size was first used to predict complications in patients with thoracic aortic aneurysms.[17] We found that an ASI ≥25 mm/m^2 in the 1st trimester is associated with a high risk for aortic dilatation or dissection during pregnancy and after birth. The ASI is a novel measurement of relative aortic size that predicts rupture of aortic aneurysm,[17] and Davies et al found that the ASI was more important than absolute aortic size in predicting aortic complications, especially in smaller women such as those in the Japanese population.[17] We found that there was more rapid growth of the sinus of Valsalva in patients with Marfan syndrome with pregnancy-associated aortic dilatation or dissection, compared to those without these conditions. Therefore, even if the diameter of the sinus of the Valsalva is small, rapid growth carries a risk of aortic dissection or dilatation. The same phenomenon has been reported in non-pregnant cases of Marfan syndrome. Meijboom et al followed 108 women with Marfan syndrome and aortic root growth prospectively using serial echocardiograms, and found that the patients could be divided into 2 normally distributed groups based on aortic growth rates: 90% had slow growths and 10% had fast growth.[15] Significantly more dissections of the ascending aorta (25% vs. 4%, P<0.001) were observed in the fast growth group, and the average growth of the sinus of Valsalva in the fast group was 1.8 mm/year. The median growth in the present 5 cases of aortic dissection was as high as 4.1 mm/year. This large increase relative to that in the Meijboom et al study[15] is probably due to the maternal cardiovascular changes in pregnancy, including increased blood volume, heart rate, and stroke volume.[25] Furthermore, hormonally mediated histological changes also occur in the aorta, including a decrease in mucopolysaccharides and loss of elastic fibers in the aortic wall.[26–28] Care is therefore required in treating patients with a high growth rate of the sinus of Valsalva. The frequency and degree of aortic and mitral valve regurgitation were also higher in patients with aortic dilatation or dissection, and these valvular changes may have been the causes of dilatation or dissection.

An international expert panel established the revised Ghent criteria in 2010, which, first, focused more on cardiovascular manifestations, and in which aortic dilatation/dissection and ectopia lentis are the cardinal clinical features.[29] Second, in these revised criteria, a more prominent role is assigned to molecular genetic testing of FBN1 and other relevant genes in the diagnostic assessment. Third, some of the less specific manifestations of Marfan syndrome were either removed or made less influential in the diagnostic evaluation of patients. The new criteria also differentiate Marfan syndrome from Marfan-related syndromes such as Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and familial thoracic aortic aneurysm syndrome, which are associated with a significantly greater risk of cardiovascular problems.[29–31] In the present study, patients with dilatation or dissection of the aorta were less likely to meet major ocular criteria, and more likely to meet the major cardiovascular criteria and had a more frequent family history of dilatation or dissection. These findings indicate that the new diagnostic criteria for Marfan syndrome facilitate identification of high-risk patients for pregnancy-associated dilatation or dissection more accurately.

Study Limitations

The disease severity of the present patients may have been higher than that of general Marfan syndrome patients because the National Cerebral and Cardiovascular Center is a referral center for cardiovascular diseases, and we also perform gene analysis.[32] Therefore, most Marfan syndrome patients are referred to our center due to cardiovascular complications and many have a family history of aortic complications. Also, because we investigated the clinical courses of Marfan syndrome patients associated with pregnancy in one institution, only 28 patients were included in the study. The small number of subjects prevented correction of the results for the effects of potential confounding factors such as hypertension, and we could not perform multifactorial analysis. The present study, however, has the advantage of clear definition of medical and surgical treatment and obstetric management. Measurements of the aorta, ventricle and atrium, and the degree of mitral and aortic valve regurgitation were also better defined in the present study compared with multi-center studies. In future research we plan to investigate a larger cohort of patients to clarify the risk factors for dilatation or dissection of the aorta in patients with Marfan syndrome during pregnancy.

Conclusion

An increased size of the sinus of Valsalva (≥40 mm) was found in Japanese patients with Marfan syndrome who experienced aortic dilatation or dissection during or after pregnancy. The ASI (size of the sinus of Valsalva/body surface area) is a better indicator of the risk for aortic dilatation or dissection during pregnancy and after birth, compared to the absolute size of the sinus of Valsalva. Until a molecular-based approach is available to identify patients at high cardiovascular risk, echocardiographic variables will remain as the most important prognostic factors. Prospective validation of the present proposed criteria is needed, but we suggest that the present strategy may be particularly useful for treatment of women with a small physique, who are common in the Japanese population.

Acknowledgments

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Disclosure

None of the authors have a conflict of interest to disclose.

References

1. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Am J Hum Genet* 1991; **49:** 662–667.
2. Keane MG, Pyeritz RE. Medical management of Marfan syndrome. *Circulation* 2008; **117:** 2802–2813.
3. Ammash NM, Sundt TM, Connolly HM. Marfan syndrome: Diagnosis and management. *Curr Probl Cardiol* 2008; **31:** 7–39.
4. Judge DP, Diez HC. Marfan's syndrome. *Lancet* 2005; **366:** 1965–1976.
5. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med* 1972; **286:** 804–808.
6. Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol* 1995; **75:** 157–160.
7. Pyeritz RE. Maternal and fetal complications of pregnancy in the Marfan syndrome. *Am J Med* 1981; **71:** 784–790.
8. Rossiter JP, Repke JY, Morales AJ, Murphy EA, Pyeritz RE. A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. *Am J Obstet Gynecol* 1995; **173:** 1599–1606.
9. Lipscomb KJ, Smith JC, Clarke B, Donnai P, Harris R. Outcome of pregnancy in women with Marfan's syndrome. *Br J Obstet Gynaecol* 1997; **104:** 201–206.
10. Lind J, Wallenburg HC. The Marfan syndrome and pregnancy: A retrospective study in a Dutch population. *J Obstet Gynecol Reprod Biol* 2001; **98:** 28–35.
11. Pacini L, Digne F, Boumendil A, Muti C, Detaint D, Boileau C, et al.

Maternal complication of pregnancy in Marfan syndrome. *Int J Cardiol* 2009; **136:** 156–161.
12. Goland S, Elkayam U. Cardiovascular problems in pregnant women with Marfan syndrome. *Circulation* 2009; **119:** 619–623.
13. Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J* 2003; **24:** 761–781.
14. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV, et al. Aortic dissection in pregnancy: Analysis of risk factors and outcome. *Ann Thorac Surg* 2003; **76:** 309–314.
15. Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJ. Aortic root growth in men and women with the Marfan's syndrome. *Am J Cardiol* 2005; **96:** 1441–1444.
16. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol* 1989; **64:** 507–512.
17. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, et al. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. *Ann Thorac Surg* 2006; **81:** 169–177.
18. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996; **62:** 417–426.
19. Roman MJ, Rosen SE, Kramer-Fox R, Devereux RB. Prognostic significance of the pattern of aortic root dilatation in the Marfan syndrome. *J Am Coll Cardiol* 1993; **22:** 1470–1476.
20. Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection. *Circ J* 2006; **70:** 1627.
21. Matsuyama K, Usui A, Akita T, Yoshikawa M, Murayama M, Yano T, et al. Natural history of a dilated ascending aorta after aortic valve replacement. *Circ J* 2005; **69:** 392–396.
22. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: Simple prediction based on size. *Ann Thorac Surg* 2002; **73:** 17–27.
23. Milewicz DM, Dietz HC, Miller DC. Treatment of aortic disease in patients with Marfan syndrome. *Circulation* 2005; **111:** e150–e157.
24. Silversides CK, Kiess M, Beauchesne L, Bradley T, Connelly M, Niwa K, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: Outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome. *Can J Cardiol* 2010; **26:** e80–e97.
25. Gandhi SD, Iqbal Z, Markan S, Almassi GH, Pagel PS. Massive retrograde acute type B aortic dissection in a postpartum woman with a family history of Marfan syndrome. *J Clin Anesth* 2008; **20:** 50–53.
26. Whittaker PG, MacPhail S, Lind T. Serial hematologic changes and pregnancy outcome. *Obstet Gynecol* 1996; **88:** 33–39.
27. Hashimoto M, Miyamoto Y, Iwai C, Matsuda Y, Hiraoka E, Kanazawa K, et al. Delivery may affect arterial elasticity in women. *Circ J* 2009; **73:** 750–754.
28. Manalo-Esrrella P, Barker AE. Histopathologic findings in human aortic media associated with pregnancy. *Arch Pathol* 1967; **83:** 336–341.
29. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, Backer JD, Devereux RC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet* 2010; **47:** 476–485.
30. Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y, Yoshimuta T, et al. Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations in the transforming growth factor-β receptor genes. *Circ J* 2007; **71:** 1305–1309.
31. Akutsu K, Morisaki H, Okajima T, Yoshimuta T, Tsutsumi Y, Takeshita S, et al. Genetic analysis of young adult patients with aortic disease not fulfilling the diagnostic criteria for Marfan syndrome. *Circ J* 2010; **74:** 990–997.
32. Toyoda T, Tateno S, Kawasoe Y, Shirai T, Shiina Y, Matsuo K, et al. Nationwide survey of care facilities for adults with congenital heart disease in Japan. *Circ J* 2009; **73:** 1147–1150.

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ORIGINAL ARTICLE
Myocardial Disease

Different Characteristics of Peripartum Cardiomyopathy Between Patients Complicated With and Without Hypertensive Disorders

– Results From the Japanese Nationwide Survey of Peripartum Cardiomyopathy –

Chizuko A. Kamiya, MD; Masafumi Kitakaze, MD, PhD; Hatsue Ishibashi-Ueda, MD, PhD; Satoshi Nakatani, MD, PhD; Toyoaki Murohara, MD, PhD; Hitonobu Tomoike, MD, PhD; Tomoaki Ikeda, MD, PhD

Background: There has been no nationwide survey concerning peripartum cardiomyopathy (PPCM) among the Asian population, and clinical profiles of PPCM complicated with hypertensive disorders complicating pregnancy (HD) as the major risk factor of PPCM have not been characterized.

Methods and Results: A retrospective, nationwide survey of PPCM in 2007 and 2008 all over Japan was performed and the clinical characteristics were compared between patients with and without HD. We obtained data for 102 patients. HD during pregnancy occurred in 42 patients (41%). Patients with HD were older than those without HD (33.8 vs. 31.9 years old, $P<0.05$) and babies were delivered more frequently by Caesarean section (81% vs. 52%, $P<0.01$). Although cardiac parameters at diagnosis were similar in patients with and without HD, patients with HD were hospitalized for a shorter period and had better cardiac function after 7 months. Multivariate regression analysis revealed that HD was independently associated with a shorter hospital stay and a higher left ventricular ejection fraction at last follow up.

Conclusions: PPCM complicated with HD had different clinical characteristics from those without HD. This condition might be a unique subset of PPCM that is characterized by relatively swift recovery except in the cases of death. In order to prevent severe heart failure and maternal death, peripartum women should be treated with HD cautiously and must immediately undergo a cardiac examination as needed. (*Circ J* 2011; **75:** 1975–1981)

Key Words: Cardiomyopathy; Heart failure; Hypertension; Pregnancy; Prognosis

Peripartum cardiomyopathy (PPCM) and pregnancy-associated cardiomyopathy are rare but life-threatening conditions that occur during the peripartum period in previously healthy women. Although its etiology remains unknown, potential risk factors include advanced maternal age, multiparity, multiple gestation, African descent, use of tocolytic agents, preeclampsia, and chronic hypertension.[1–3] Next to African descent, Asian populations showed the second highest incidence of PPCM in a study performed in Southern California,[4] but there was no nationwide survey about PPCM in Asian counties. Hypertensive disorders complicating pregnancy (HD) are observed in up to 60% of PPCM patients,[5] but few studies have analyzed the differences in clinical characteristics between PPCM patients with and without HD. Therefore, this study was performed: (1) to characterize PPCM in Japanese women; and (2) to evaluate whether complications of PPCM with hypertension affects the prognosis for this condition.

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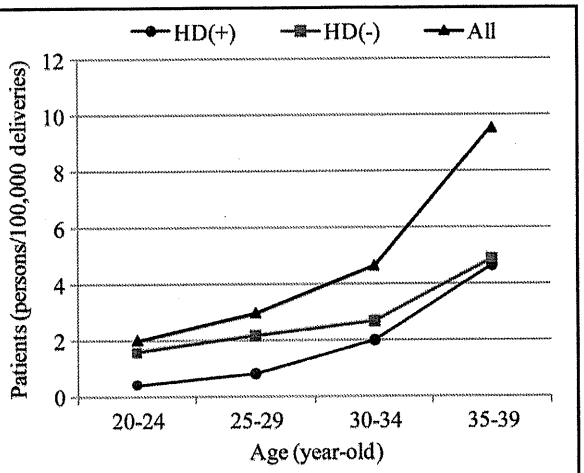

Figure 1. Incidence of PPCM per 100,000 deliveries in each age group. PPCM, peripartum cardiomyopathy; HD, hypertensive disorders complicating pregnancy.

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Methods

A questionnaire survey of 1,444 professional medical organizations in Japan, including 1,030 departments of cardiology, 1,025 departments of obstetrics, and 431 emergency departments, was performed to identify patients with PPCM who were newly managed from January 2007 to December 2008. The diagnosis of PPCM was based on the following criteria: (1) development of heart failure during pregnancy or within the first 5 postpartum months; (2) no determinable etiology for cardiac failure; (3) no history of heart disease prior to pregnancy; (4) reduced left ventricular contraction based on a left ventricular ejection fraction (LVEF) <50% and/or a percent fractioning shortening (%FS) <30%. We modified the criteria established by Demakis and Rahimtoola[1] and those recommended by a workshop convened by the National Heart Lung and Blood Institute and the Office of Rare Diseases of the National Institute in Health.[6] Although classic diagnostic criteria of PPCM by Demakis and Rahimtoola limited the diagnosis to the last gestational month and first 5 months after delivery, Elkayam et al reported that clinical presentation and outcome of patients diagnosed early in pregnancy were similar to those of patients with traditional PPCM.[7] We included patients who developed heart failure during pregnancy and during the first 5 months after delivery in the present study, which was based on the report by Elkayam et al.

Age, parity, complications of pregnancy, time of diagnosis, symptoms, time and route of delivery, outcomes of mother and infant, length of hospital stay, and therapeutic information were collected as background data. Echocardiographic parameters and serum brain natriuretic peptide (BNP) levels at diagnosis, at hospital discharge, and at the last follow up were also obtained. If the patients were complicated with HD, the type and severity of hypertension, and the duration between the onset of HD and diagnosis of PPCM were also recorded.

HD were categorized according to the National High Blood Pressure Education Program Working Group Report on high blood pressure (BP) in pregnancy as: (1) gestational hypertension: systolic BP≥140 mmHg or diastolic BP≥90 mmHg for the first time during pregnancy, and no proteinuria (PU); (2) preeclampsia: systolic/diastolic BP≥140/90 mmHg after 20 weeks' gestation and PU≥300 mg/day or ≥1+dipstick; (3) eclampsia: seizures that cannot be attributed to other causes in a woman with preeclampsia; (4) preeclampsia superimposed on chronic hypertension: new-onset PU≥300 mg/day in hypertensive women without PU before 20 weeks' gestation or a sudden increase in PU or BP in women with hypertension and PU before 20 weeks' gestation; and (5) chronic hypertension: systolic/diastolic BP≥140/90 mmHg before pregnancy or diagnosed before 20 weeks' gestation.[8] The severity of preeclampsia was defined as mild for systolic/diastolic BP ≥140/90 mmHg and severe for systolic/diastolic BP≥160/110 mmHg. PU was defined as mild for >300 mg/day and severe for >2.0 g/day. The number of deliveries in Japan in

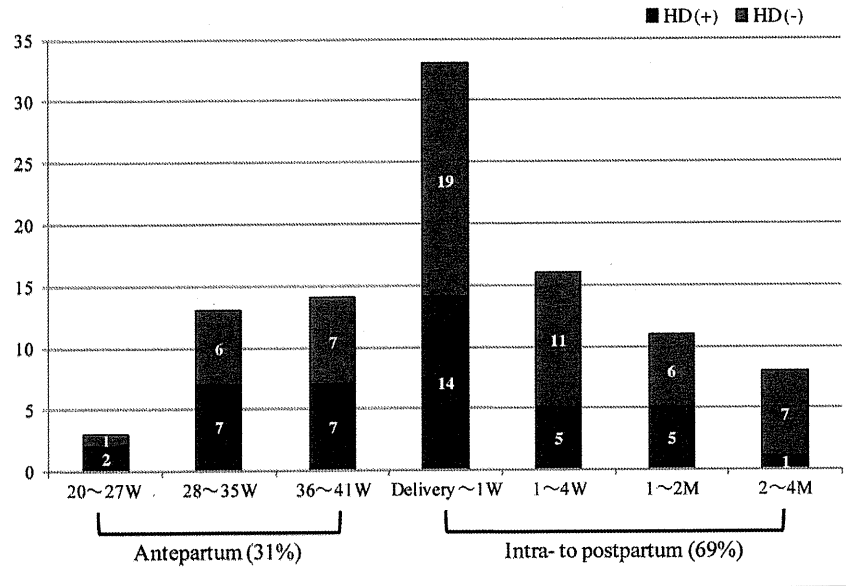

Figure 2. Time of diagnosis. HD, hypertensive disorders complicating pregnancy.

Table 1. Comparison of Patients' Background and Use of Medications at Discharge Between PPCM Patients Complicated With and Without HD

	HD (+) (n=42)	HD (–) (n=60)	P value*
Age (years)	33.8±4.2	31.9±4.1	<0.05
Parity	1.62±1.17	1.67±0.78	NS
Tocolytic therapy	6	8	NS
Twin pregnancy	7	8	NS
HD	42 (100%)	0	<0.0001
Gestational weeks of delivery (weeks)	36.4±3.7	37.5±2.4	NS
Route of delivery			
Vaginal delivery	8	27	<0.01
Cesarean section	34	29	
Medications at discharge			
ACE-I/ARB	26 (67%)	33 (63%)	NS
β-blocker	22 (56%)	30 (58%)	NS
Diuretics	26 (67%)	29 (56%)	NS
Anticoagulant	11 (28%)	11 (21%)	NS

PPCM, peripartum cardiomyopathy; HD, hypertensive disorders complicating pregnancy; NS, not significant; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*P value for comparison of the HD (+) and HD (–) groups.

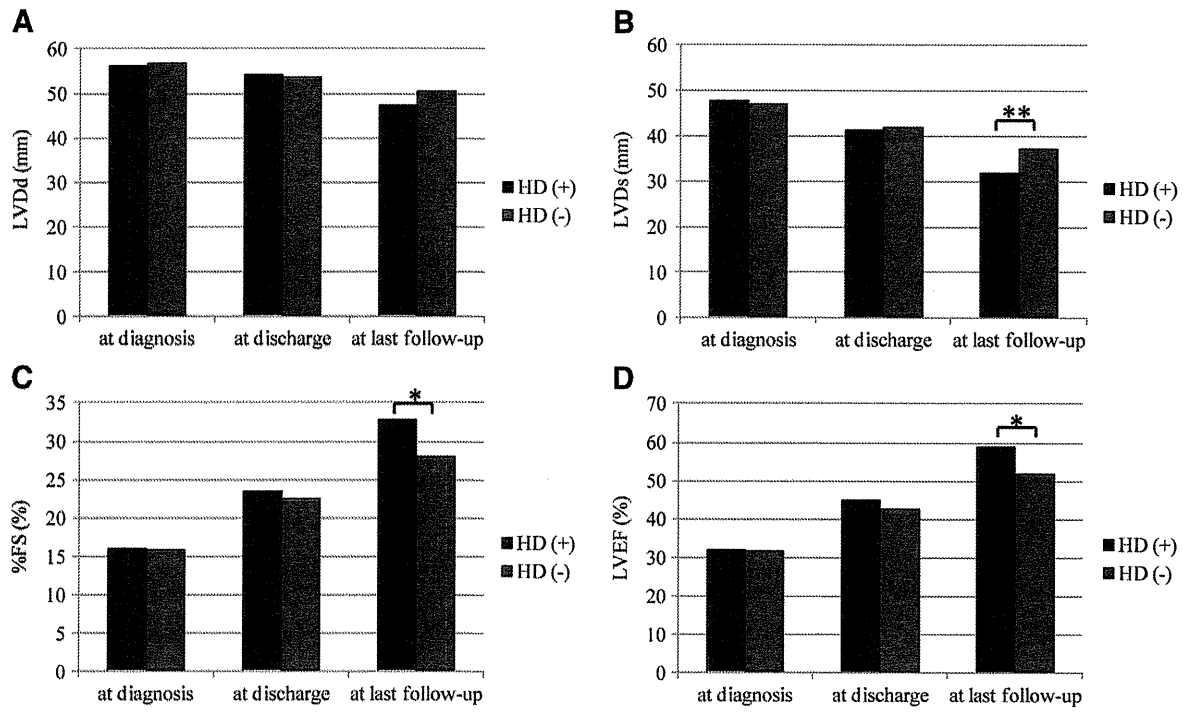

Figure 3. Changes of (**A**) LVDd, (**B**) LVDs, (**C**) %FS, and (**D**) LVEF in HD (+) and HD (–) groups. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; %FS, % fractional shortening; LVEF, left ventricular ejection fraction; HD, hypertensive disorders complicating pregnancy. *P<0.05 for comparison of the HD (+) and HD (–) groups. **P<0.01 for comparison of the HD (+) and HD (–) groups.

each age group were taken from national statistics published by the Ministry of Health, Labour and Welfare.

Statistical significance was evaluated using paired and unpaired Student t-tests for comparisons between means. A chi-square test and a Fisher exact test were used for categorical data. Two-way ANOVA and correlation coefficient analysis were also used. Multivariate analysis was done to examine the correlations of length of hospital stay and LVEF at last follow up with variables such as age, parity, time of diagnosis, tocolytic therapy, twin pregnancy, HD and LVEF at diagnosis, which are considered as risk factors. All data were expressed as the mean±standard deviation. Statistical signifi-

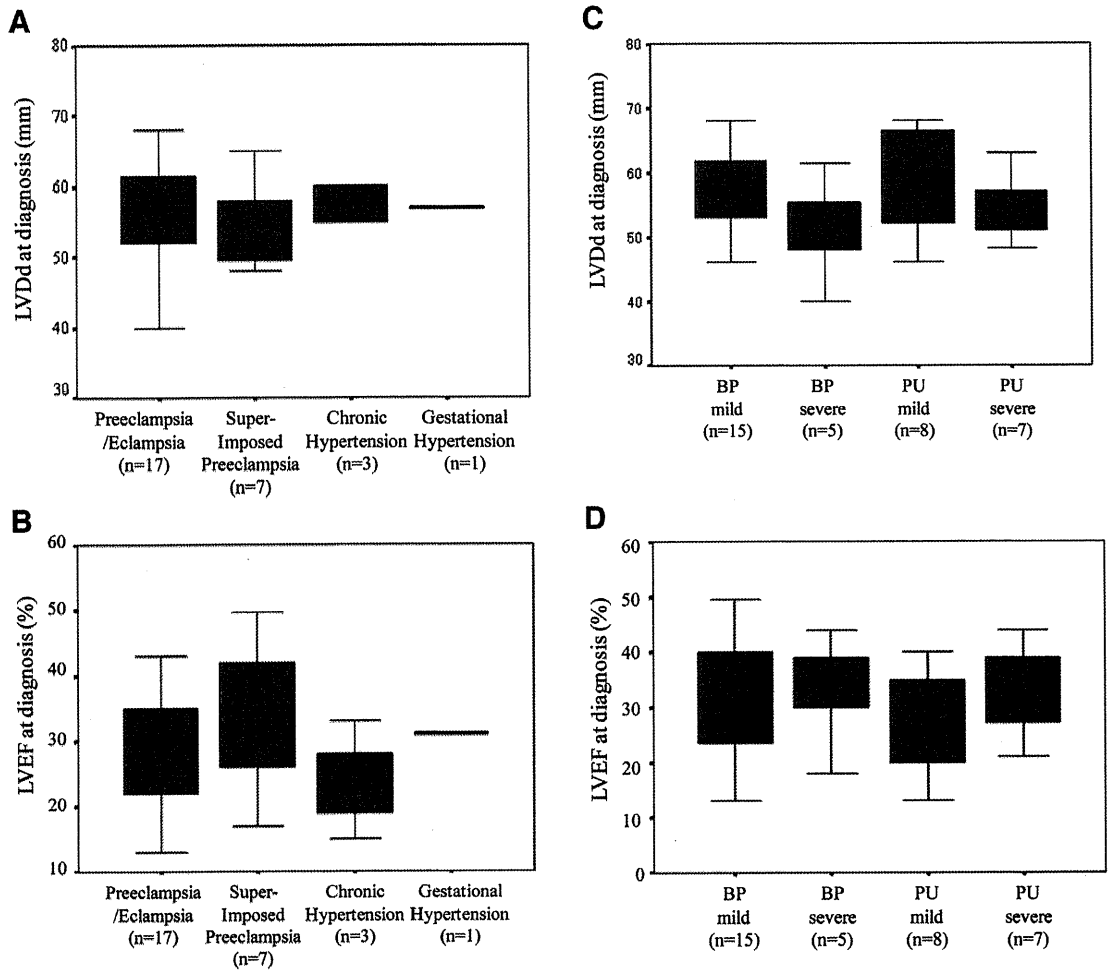

Figure 4. (**A**) LVDd and (**B**) LVEF at diagnosis in each type of HD, and (**C**) LVDd and (**D**) LVEF at diagnosis in preeclampsia patients with different severities of BP and PU. HD, hypertensive disorders complicating pregnancy; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; BP, blood pressure; PU, proteinuria.

cance was defined as a P value <0.05. A software package (SPSS 11.0; SPSS, Chicago, IL, USA) was used for statistical analysis.

The Ethics Committee at the National Cerebral and Cardiovascular Center in Osaka, Japan approved the study in November 2008.

Results

Clinical Characteristics of All Patients

Out of 1,444 institutes, 1,049 (73%) responded. These responses included 102 cases fulfilling the inclusion criteria for PPCM. The estimated incidence of PPCM in Japan was 1/20,000 births. The mean age of the patients was 32.7 years old, with a range of 22–43 years old. Fifty-four percent of patients were primiparous women and the mean parity was 1.65±0.96. Tocolytic agents were used during pregnancy in 14%, twin pregnancy occurred in 15%, and HD was present in 42% of PPCM patients.

Diagnosis of PPCM was established antepartum in 31% and intra to postpartum in 69%. One-third of patients were diagnosed intrapartum to within 1 week after delivery. The major symptoms at onset were dyspnea in 80%, cough in 37%, and edema in 37%. With those complaints, 63% of patients were initially seen by an obstetrician and 12% of patients were seen by a general physician, and then referred to cardiologists. Only 9% were primarily seen by a cardiology specialist.

At diagnosis, an echocardiography showed the following mean values: left ventricular end-diastolic dimension (LVDd) 56.5±7.1 mm, left ventricular end-systolic dimension (LVDs) 47.8±8.1 mm, %FS 15.8±7.0%, and LVEF 31.6±12.0%. The mean serum BNP level was elevated to 1,258±1,028 pg/ml. There were only 4 patients whose serum BNP level was under 100 pg/ml.

The mortality rate was 4%. One patient who was at 34 weeks' gestation died from pulmonary edema on the day of admission, 1 patient died from acute heart failure 1 day after an emergency Caesarean section was performed because of obstructed labor at 37 weeks' gestation, 1 died from cardiac arrest 2 days after vaginal delivery despite implementation of percutaneous cardiopulmonary support, and another died