特集　事例から学ぶ妊産婦死亡の予防対策

弛緩出血
—DIC先行羊水塞栓症—

金山 尚裕

羊水塞栓症の病因は羊水成分が母体循環系へ流入し，塞栓あるいはアナフィラクトイド反応が発生することである。初発症状から心肺虚脱症状が前面に出るものを全身型，DIC型と分類される。前者は全身型羊水塞栓症，後者はDIC先行羊水塞栓症と分類されるが，後者は弛緩出血，非凝固性の子宮出血が主たる症状であるので子宮型羊水塞栓症とも呼ばれる[1]。本稿では弛緩出血DIC主体の羊水塞栓症を子宮型羊水塞栓症と呼ぶ。子宮型羊水塞栓症の病因は羊水によるアナフィラクトイド反応と考えられている。その機序は以下のように考えられている。羊水が子宮筋の裂傷部位や子宮内腔に露出した破綻血管と接触する。羊水と母体組織が接触しても多くの症例で変化を起こさないが，症例によっては羊水により母体免疫系が過剰に活性化し，アナフィラクトイド反応が惹起される。その結果DICが発生する症例がある。

事例概要

34歳，G2P21

妊娠37週4日：反復帝王切開施行。児の娩出後子宮収縮薬にても良好な子宮収縮が起こらず，子宮筋縫合中に非凝固性のサラサラした出血となる。創部および子宮内腔からの出血が急激に増加した。オキシトシン局注，麦角剤の投与でも弛緩出血改善せず。この時のフィブリノゲン55 mg/dL，血小板数19万/μLオキシトシン，D-dimer 230 μg/mL。娩出後1時間で出血量3,000 mL，DICショックとなる。RCCをまず投与したが，出血は増量した。FFPを15単位投与，抗DIC対策としてアンチトロンビン3,000単位静注，ウリナスタチン30万単位静注，トラネキサム酸2 g点滴投与したところでショックは改善し，止血傾向となった。子宮弛緩症は継続していたため，子宮全摘施行術施行。その後もFFP投与，抗DICを継続し，DICは収束した。

分娩後3週間：退院。なお，発症時の羊水マーカーの亜鉛コプロポルフィリン-1，STNはいずれも陰性であった。C3：45 mg/dL，C4：5 mg/dLで低値であり，IL-8は520 pg/mLと高値であった。

事例の解説

▷本症例は典型的子宮型羊水塞栓症である。

▷上記検査所見を踏まえて臨床的羊水塞栓症の診断を行う。臨床的羊水塞栓症の診断基準は以下のようになっている。

①妊娠中または分娩後12時間以内に発症した場合

②下記に示した症状・疾患（一つまたはそれ以上でも可）に対して，集中的な医学治療が行われた場合

A）心停止

B）分娩後2時間以内の原因不明の大量出血（1,500 mL以上）

C）播種性血管内凝固症候群

D）呼吸不全

③観察された所見や症状がほかの疾患で説明できない場合

以上の三つを満たすものを臨床的羊水塞栓症と診断する。特に②のA）やD）がなく主体がB），C）であるものは子宮型羊水塞栓症と判断してもよい。

▷検査としては，分娩時に非凝固性の子宮出血を認めたらまずDICを考え，以下の検査を行う。まずフィブリノゲンとD-dimer，CBCを測定する。

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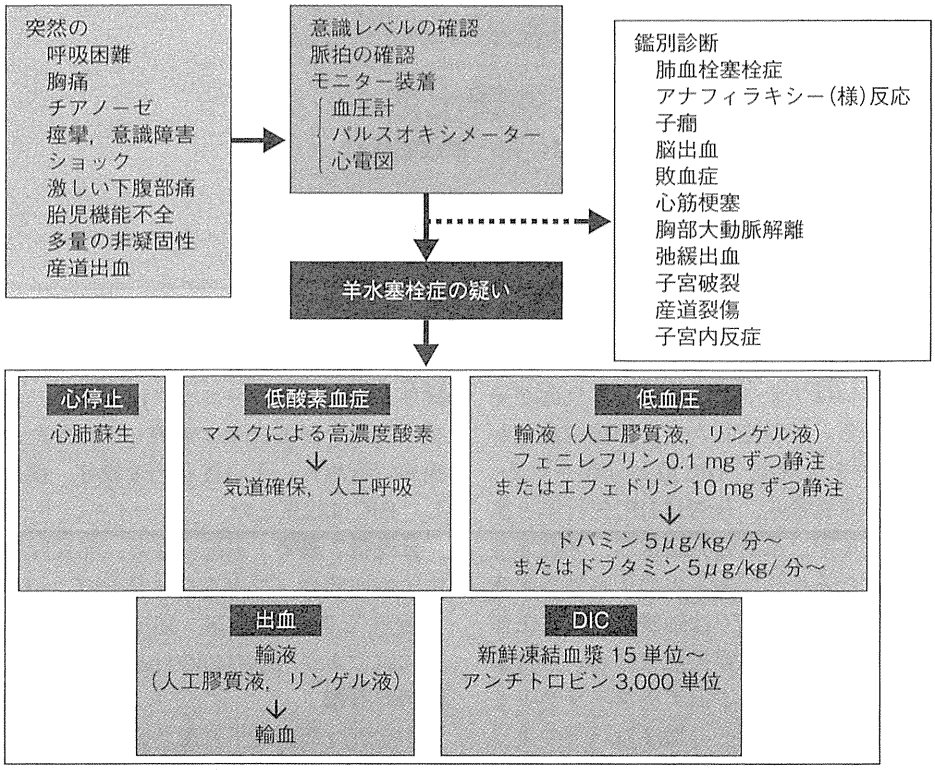

図1　羊水塞栓症の初期対応（妊産婦死亡症例検討評価委員会，日本産婦人科医会編）

※心肺虚脱型の羊水塞栓症では，肺塞栓血栓症とアナフィラキシー(様)反応の鑑別が困難であり，この2者も念頭に置いた対処が必要である

※痙攣が認められた場合には，ジアゼパム5～10 mgまたはミダゾラム2～5 mgを静注する

※羊水塞栓症はアナフィラキシー(様)反応と類似した病態であることも示唆されており，副腎皮質ステロイドの投与を考慮すべきである

※診断のためには，フィブリノゲン，血小板，Dダイマーの測定が特に重要である

※STNやZnCP1などの測定のため，2～3 mL程度の血清を遮光凍結保存しておく

続いて補体C3，C4を測定する。フィブリノゲンが極端な低値(100 mg/dL以下)，D-dimer高値(50 μg/mL以上)，C3，C4低値(C3 80 mg/dL以下，C4 12 mg/dL以下)，IL-8高値(20 pg/mL以上)の時は羊水塞栓症，特に子宮型を疑う。

▷リアルタイムには結果は出ないが，後に検証するために母体血中への羊水マーカー検出は重要である。羊水固有物質を母体血中で捉える方法で亜鉛コプロポルフィリン1(zinc coproporphirin1：Zn-CP1)やシアリルTn(STN)が使用される。なお，亜鉛コプロポルフィリン1は光で変成するため，採血後は血清にしてアルミ箔などを用いて遮光することが大切である。心肺虚脱型ではこれらが高値を示す。子宮型ではこれらの羊水マーカーが検出されないことが多い。

◆初期対応

羊水塞栓症をはじめとする産科ショックでは初期対応と並行してマンパワーを集めることと，可及的速やかにICUに移動させ管理することが大切である。鑑別診断および羊水塞栓症の初期対応としては妊産婦死亡症例評価委員会(代表 池田智明)の「母体安全への提言2011 Vol.2」[2]に記載してあることを忠実に行う(**図1**)。全身型の羊水塞栓症では未だに救命することが困難な症例も多数あるが，迅速な初期対応は予後を大きく左右する。子宮型羊水塞栓症はDICの早期対応によって救命率は上がる。

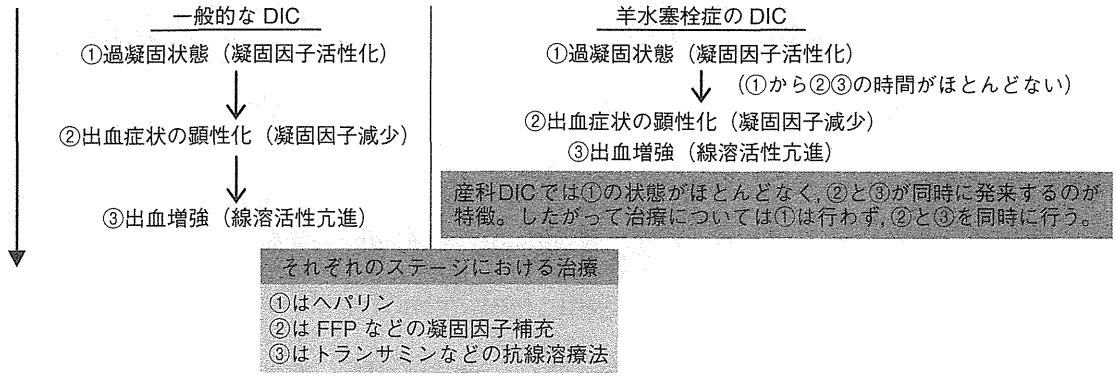

図2　羊水塞栓症によるDICの特徴

◆ DIC対策

DIC対策のポイントは，凝固因子の早期からの大量補充と大量の抗線溶療法である。羊水塞栓症のDICは凝固の亢進と線溶の亢進が劇的に進行するので，両者に対して十分な治療を行うことがポイントである。羊水塞栓症のDICの特徴を**図2**に示した。

羊水塞栓症では凝固因子の消費とともに線溶の顕著な亢進が特徴である。したがって羊水塞栓症によるDICでは凝固因子の補充と線溶因子の補充，同時に凝固抑制，線溶抑制を図る必要がある。凝固因子の補充と線溶因子の補充はFFPで，凝固抑制はアンチトロンビンで，線溶抑制はトラネキサム酸やウリナスタチンで行う。欧米では後産期DICの治療にトラネキサム酸の大量投与が一般的に行われており，線溶亢進型DICの多い産科DICでは有効性が高い[3]。

具体的なDICの治療内容は下記に示した。

◆ DIC療法の実際

1）FFP（10～15単位）とアンチトロンビン3,000単位投与，RCC-LR投与は出血の程度で決める
2）その後は検査・症状をみながら輸血，FFP：RCC比1.5以上を目指す
3）血小板は病態を考慮して投与を考える
4）ウリナスタチン30万単位投与，トラネキサム酸2～4 g投与（1時間程度で）
5）ステロイド大量静脈投与（発症早期に投与することが重要：500～1,500 mg），FOY等は適宜投与

上記を早期に行えば，ほとんどのDIC症例で改善が得られるが，それでも難渋する症例はノボセブン（factor VII）1V（4.8 mg）静脈投与を考慮する。

◆輸血療法

DIC，大量出血時は異型適合輸血をためらわない。急ぐ時には，具体的にはO型RCC，AB型FFP投与を行う。またFFPの早期からの大量投与が重要で，血小板濃厚液は必ずしも初期より投与する必要はない。

◆外科療法

薬物療法で十分な止血効果が得られない場合，外科的方法を考慮する。まず子宮腔内のバルーンタンポナーデを挿入し，出血が減少するかみる。バルーンタンポナーデ法にて効果が得られなければ，子宮動脈塞栓術も考慮する。しかし，羊水塞栓症は多くの場合アナフィラトキシンが子宮に大量発生していることが多く，子宮全摘術によって子宮に含まれる大量のアナフィラトキシンが除去され，病態が改善に向かうことも多い。

文献

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症例報告

胃巨大皺襞症を呈し10年間の経過観察中に粘膜下腫瘍様進行胃癌を発症したdiffuse cystic malformationの1例

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要旨：症例は66歳男性．2000年2月より胃巨大皺壁症にて経過観察していたが，2010年3月胃体上部大弯に直径35mmの粘膜下腫瘍様隆起を認めた．超音波内視鏡下穿刺吸引針生検による病理診断後胃全摘術を行い，diffuse cystic malformation（DCM）より発生した粘膜下腫瘍様進行胃癌と診断した．DCMはまれな疾患であり，びまん性粘膜下異所性胃腺との異同や胃癌との関連について考察し報告する．

索引用語：胃巨大皺襞症，diffuse cystic malformation，粘膜下異所性胃腺

背　景

胃粘膜固有層ないし粘膜下層に多発嚢胞性病変を認める疾患は，海外ではdiffuse cystic malformation（DCM）[1)~4)]，国内ではびまん性粘膜下異所性胃腺[5)6)]として報告されてきたが，その異同についてはあまり論じられてこなかった．今回われわれは巨大皺襞症を呈し長期経過観察中に粘膜下腫瘍進行癌を発症したDCMの1例を経験し，文献的にDCMとびまん性粘膜下異所性胃腺の共通点と相違点を整理した．胃癌を高率に合併することは臨床上重要な共通点であるが[4)~9)]，DCMと発癌の関連性や経過観察の方法についても考察した．

I　症　例

患者：66歳男性．

主訴：胃重感．

既往歴：2006年高血圧，高尿酸血症，2009年大腸癌外科手術（Stage I）．

生活歴：喫煙歴なし．飲酒はビール700ml/日．

現病歴：2000年2月健診の上部内視鏡検査で胃巨大皺襞症を認め（Figure 1a），生検や超音波内視鏡検査にて悪性リンパ腫や4型胃癌などの腫瘍性病変を除外した．超音波内視鏡検査では肥厚した第2層内に小嚢胞病変を認めたが，肥厚性胃炎による腺管拡張に矛盾ないものとして，以後主に通常の内視鏡検査で経過観察していた．それまで無症状であったが2004年頃より胃重感を自覚するようになった．2006年にヘリコバクター・ピロリ除菌に成功，2007年胃体部大弯巨大皺襞に対して超音波内視鏡下穿刺吸引針生検（endosonography-guided fine needle aspiration；EUS-FNA）を行うも腺窩上皮のみで，腫瘍性病変を疑う所見を認めなかった．2010年2月血液検査にてCA19-9 404U/mlと上昇を認めた．

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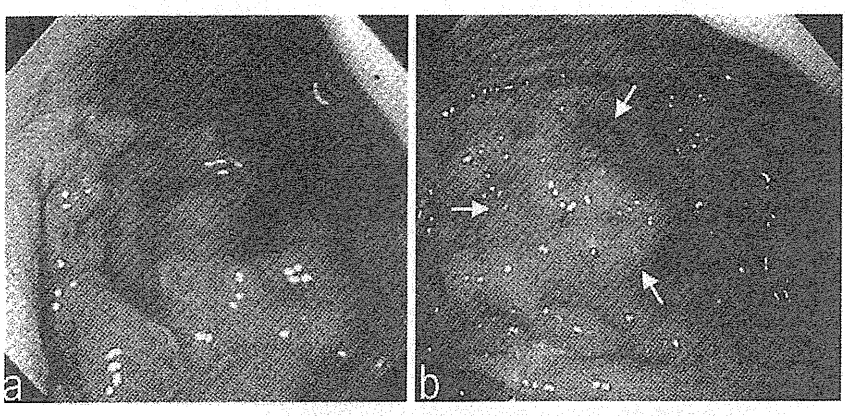

Figure 1. (a) 2000年2月の胃内視鏡所見．胃体部大弯に巨大皺襞を認めた．(b) 2010年3月の胃内視鏡所見．胃体部大弯の巨大皺襞に加え胃体上部大弯に直径約35mmの粘膜下腫瘍様隆起が見られた（矢印）．

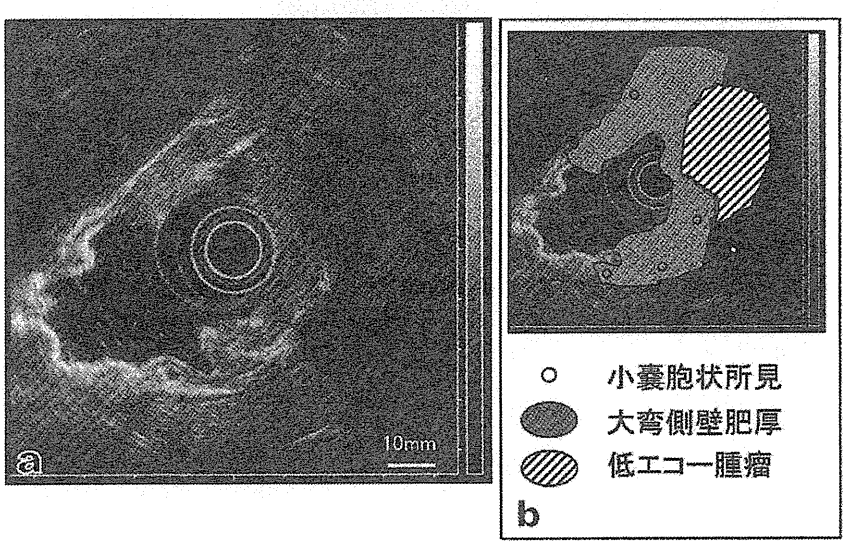

Figure 2. (a) 胃超音波内視鏡所見（オリンパス GF-UM2000）．胃体部大弯，広範囲の第2層の著明な肥厚と小嚢胞像を認めた．胃体上部大弯壁内に第2～5層に及ぶ直径30×25mmの辺縁不整な低エコー腫瘤を認めた．(b) aのシェーマ．

2010年3月上部内視鏡検査：以前より認めていた巨大皺襞症に加えて，胃体上部大弯に直径35mmの粘膜下腫瘍を認めた（Figure 1b）．表面に明らかな潰瘍，びらんや腫瘍の露出は認めなかった．病変表層粘膜からの生検で得られた組織は異型の乏しい腺窩上皮のみであった．

胃超音波内視鏡検査（endoscopic ultrasonography；EUS，Figure 2）：胃体部大弯，広範に第2層の著明な肥厚とその内部に散在する2～3mmの嚢胞を認める点は2000年と著変なかった．胃体上部大弯の粘膜隆起部位に一致して30×25mm，辺縁不整で第2～5層に及ぶほぼ均一な低エコー腫瘤を認めた．また第5層は一部で不明瞭となっており腫瘍の漿膜浸潤が疑われた．

上部消化管バリウム造影検査（Figure 3a，b）：胃体部大弯広範に表面不整多発結節状隆起を，胃

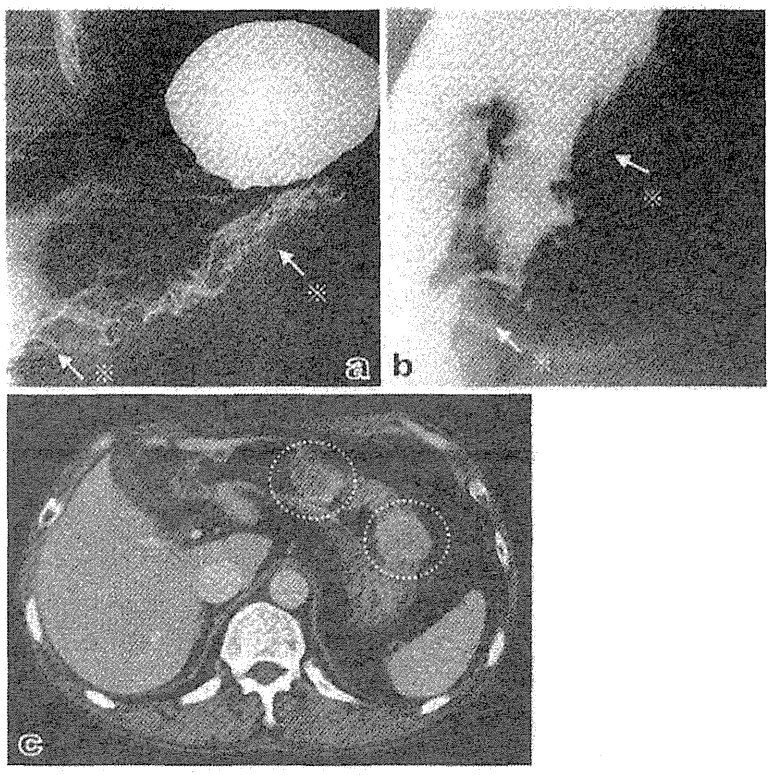

Figure 3. 上部消化管バリウム造影所見：(a) 背臥位二重造影像．(b) 背臥位充盈圧迫像．いずれも胃体中上部大弯広範に表面不整多発結節状隆起を認めた．胃体上下部にそれぞれ粘膜下腫瘍様隆起を認めた(※矢印)．(c)腹部造影CT所見．胃体上部（30×25mm）と胃体下部にそれぞれ造影効果を有する腫瘤を認めた（点線円）．

体上下部大弯それぞれに粘膜下腫瘍様隆起を認めた．胃壁の伸展性は比較的保たれていた．

腹部造影CT（Figure 3c）：胃体上部（30×25 mm）と胃体下部に，それぞれに造影効果を有する腫瘤を認めた．周囲のリンパ節に明らかな腫大は認めなかった．

確定診断のため，2010年4月EUS-FNA目的で入院となった．

入院時現症：身長162.2cm，体重55.9kg，血圧130/72mmHg，脈拍70/分・整，腸蠕動音良好，腹部平坦軟，圧痛なし．その他特記すべき所見なし．

入院時血液検査（Table 1）：検血，生化学検査値に異常なし．CA19-9が高値であった．

EUS-FNA所見（Figure 4）：胃体上部大弯の粘膜下腫瘍の病理診断目的でEUS-FNAを施行した．病理所見では腫大した核内に大型の核小体を有する異型性の強い腺癌細胞を認めた．

それにより粘膜下腫瘍様進行胃癌cT4a（SE）N0M0，Stage IIBと診断し外科手術を行った．

2010年5月外科手術：開腹下に胃全摘術，胆嚢摘出術，脾臓摘出術，リンパ節D2郭清，Roux-en-Y再建術を施行した．

切除標本の肉眼所見：小弯切開にて展開した固定前の切除胃のサイズは25.0×16.0cmで，胃体部大弯12.0×9.5cmの範囲に表面不整で結節状に隆起した壁肥厚を認めた（Figure 5）．壁の厚さは最大35mmで硬さは弾性やや軟であった．胃体上部大弯には35×35mmの粘膜下腫瘍様隆起が見られた（Figure 5）．その肛門側，胃体下部

Table 1. 入院時血液検査所見

検血		ALT	18 IU/l	T-CHO	145 mg/dl
WBC	6690 /μl	ALP	294 IU/l	TG	95 mg/dl
RBC	469万 /μl	γ-GTP	77 IU/l		
Hg	15.9 g/dl	Ch-E	217 IU/l	凝固系	
PLT	15.9万 /μl	LDH	201 IU/l	PT	11.9 s
		CK	78 IU/l	INR	1.00
生化学		BUN	13.7 mg/dl	APTT	27 s
TP	7.0 g/dl	CRE	0.83 mg/dl		
ALB	4.0 g/dl	CRP	1.3 mg/dl	腫瘍マーカー	
T-BIL	0.4 mg/dl	Na	142 mEq/l	CEA	4.4 ng/ml
D-BIL	0.1 mg/dl	K	3.8 mEq/l	CA19-9	355 U/ml
AST	27 IU/l	Cl	103 mEq/l		

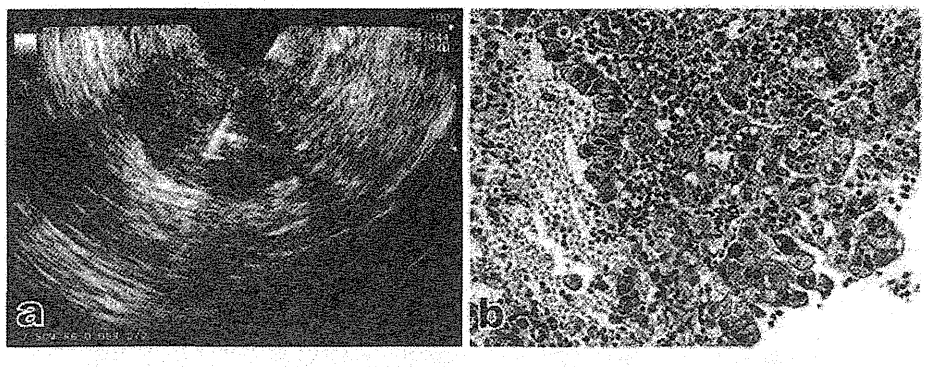

Figure 4. (a) 胃体上部大弯粘膜下腫瘍に対するEUS-FNA穿刺時の超音波内視鏡像．均一低エコー腫瘤内に穿刺針が確認できる．使用機種はUCT240-AL5，穿刺針はNA-200H-8022（いずれもオリンパス）．(b) EUS-FNAにて採取した検体の病理所見．腫大した核と大型の核小体を有する異型の強い腺癌細胞を認める（HE染色×400）．

にも直径約20mm大の粘膜下腫瘍様隆起が見られた．

切除標本の病理組織所見：ルーペ像では胃体上部大弯の粘膜下腫瘍様隆起の内部に固定標本上1.9×1.7cmの粘膜下腫瘍様病変が見られた（Figure 6a，b）．強拡大では核の腫大と腺管構造の乱れ，乳頭状の増殖を示す腺癌の所見を認めた(Figure 6c)．胃癌周囲の胃体部大弯，広範の胃壁肥厚部の粘膜固有層～粘膜下層にはびまん性に数100μm～4mmの多数の嚢胞状拡張腺管と間質の増生を認め（Figure 6d），それにより胃体下部大弯の粘膜下腫瘍様隆起や壁肥厚が形成されていたと考えられた．多発嚢胞病変を裏装する腺細胞は1層の円柱～立方上皮からなる粘液腺で，内部に淡赤色の粘液が見られることもあった．多発嚢胞は周囲を平滑筋線維で包囲されていた．肥厚のない胃壁には嚢胞状変化は見られず病理学的に正常であった．また胃粘膜は萎縮性変化に乏しく，腸上皮化生も見られなかった．以上より高～中分化型管状腺癌，中間型，INFβ，SS，ly0，v0，PM（－），DM（－），pT3N0M0，pStage IIA，および胃体部大弯広範のDCMと病理学的に最終診断した．

胃壁肥厚部の粘膜筋板の走行や嚢胞周囲の平滑筋線維を確認するため，粘膜下腫瘍様胃癌の肛門側の隆起部の標本に対してα平滑筋アクチン（α-SMA）染色を施行したところ，粘膜筋板の走行は追えず本来の粘膜固有層，粘膜下層に平滑筋線

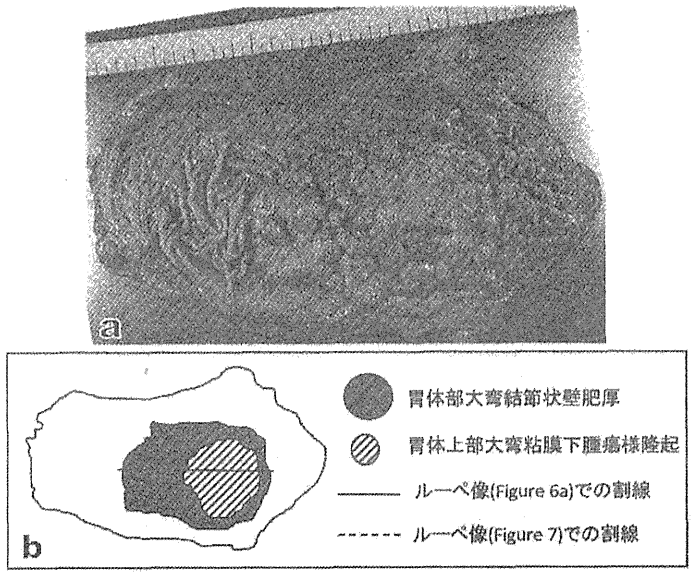

Figure 5. (a) 小弯切開した胃全摘切除標本．胃体部大弯に結節状多発隆起による壁肥厚（灰色部）を認め，胃体上部（斜線部）および体下部大弯には粘膜下腫瘍様隆起を認める．実線と点線でそれぞれ Figure 6a と Figure 7 の切り出し線を示す．(b) a のシェーマ．

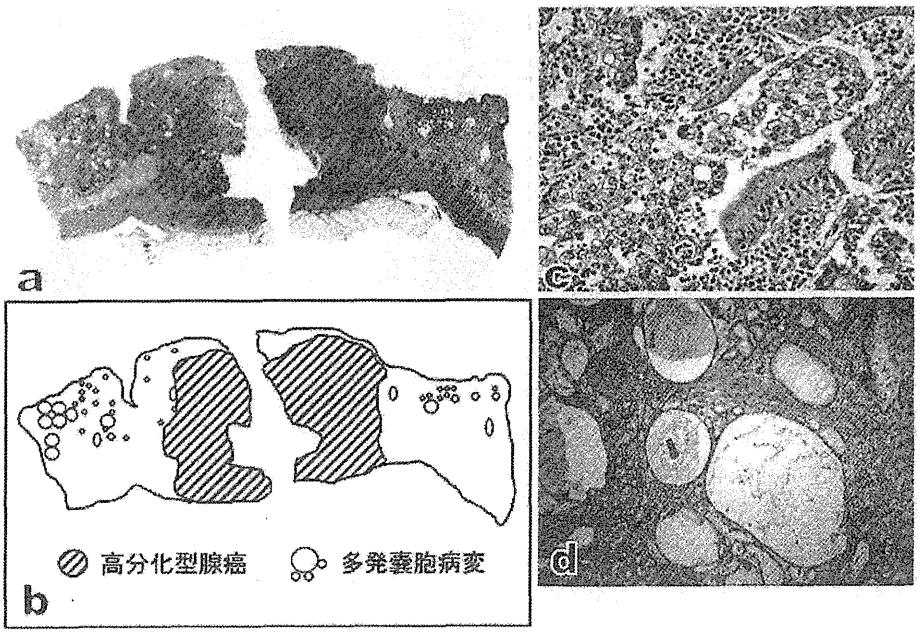

Figure 6. (a) 粘膜下腫瘍様胃癌の病理所見．Figure 5 に実線で示す切出し線に相当するルーペ像（HE 染色×1.5）．粘膜下に漿膜に達する粘膜下腫瘍様進行癌を認めた（b の斜線部）．腫瘍周囲には多発嚢胞病変を認めた．(b) a のシェーマ．(c) 腫瘍部の病理組織所見．核の腫大と腺管構造の乱れを示し，充実性に増殖する高～中分化腺癌が腫瘍の主体を成していた（HE 染色×400）．(d) 胃体部大弯，粘膜下腫瘍様胃癌周囲の結節状壁肥厚部には広範に多発嚢胞病変が見られた（HE 染色×40）．

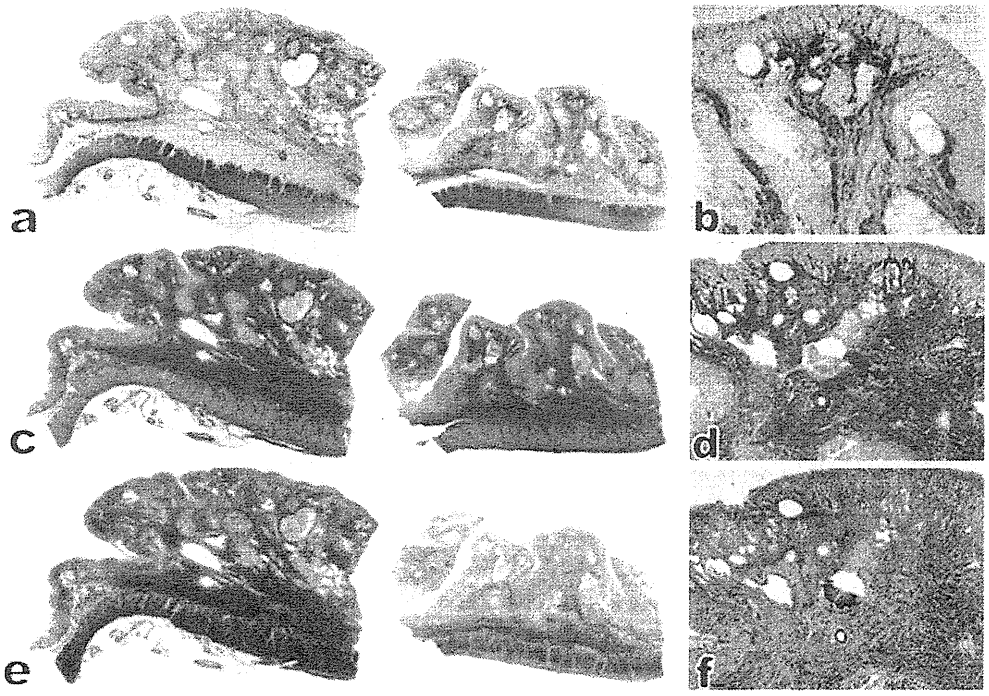

Figure 7. 粘膜下腫瘍様胃癌の肛門側．Figure 5に点線で示す切出し線に相当する免疫染色像：(**a, b**) α平滑筋アクチン（α-SMA）染色．胃壁肥厚部において粘膜筋板の走行は追えず，本来の粘膜固有層，粘膜下層と思われる部位に比較的広範に平滑筋線維の増生が見られた．(**c, d**) エラスチカ・ワンギンソーン染色．粘膜固有層相当部に黒紫色に染色される弾性線維，粘膜下層相当部に赤色に染色される厚い膠原線維増生を認める．(**e, f**) アザン染色．粘膜下層相当部に膿青色に染色される厚い膠原線維増生を認める．**a, c, e**：×1.5，**b, d, f**：×10.

維のびまん性増生が認められた（Figure 7a，b）．また今回われわれはHE染色で，多発嚢胞のみならず間質の線維性増生が胃壁肥厚の一因となっていたことに着目し，それらを病理学的に同定するためエラスチカ・ワンギンソーン染色（Figure 7c，d）とアザン染色（Figure 7e，f）を施行した．結果は本来の粘膜固有層付近に弾性線維，粘膜下層付近に著明な膠原線維の増生が見られ，特に固有筋層に接して膠原線維が3～5mm厚に密に増生しており，胃体部大弯の著明な壁肥厚の一因と思われた．

術後は順調に経過，退院し現在も再発なく通院している．また，CA19-9は術後低下し正常値を維持している．

II 考　察

本例は胃巨大皺襞症の長期経過観察中に粘膜下腫瘍様進行胃癌を発症し，外科手術を行った症例である．手術標本の病理学的検索では胃体部大弯の広範囲の粘膜固有層，粘膜下層にびまん性に多発する嚢胞性病変と間質の線維性増生を認め，著明な胃壁肥厚の原因となっていた．

海外において多発嚢胞性変化のため広範囲に胃壁の肥厚を認める疾患はScottら[1]，Obermanら[2]，Tchertkoffら[3]，Ignatiusら[4]により，diffuse congenital hyperplasia[1]やdiffuse heterotopic cystic malformation[2]などとして報告されている．過去の報告一覧をTable 2に示す．高齢の男性に多く，主に胃体部大弯の粘膜固有層から粘膜下層に多発する数mm大の嚢胞病変が特徴的所見であり[7]，それにより比較的広範囲に胃壁の肥厚を認めるとされ，本例は同様の病態と考えられる．

一方国内においては，粘膜下に10カ所以上の

Table 2. DCM の報告例

	症例数	年齢	性別	胃壁肥厚部位	嚢胞の存在する層	癌の合併	早期・進行癌	癌の肉眼型
Scott ら[1]	1	58	M	胃体中部～幽門，特に前庭部大弯	粘膜固有層・下層	なし	−	−
Oberman ら[2]	1	54	M	噴門から胃体中部の大弯主体	粘膜固有層・下層	なし	−	−
Tchertkoff ら[3]	1	21	F	噴門下小弯	粘膜固有層	なし	−	−
Ignatius ら[4]	1	43	F	胃近位側半	粘膜固有層・下層	あり	進行	潰瘍形成型
Hizawa ら[7]	9	61～75	M：F＝7：2	主に体部	粘膜固有層・下層	2/9	早期	IIa, IIc
吉満ら[8]	3	58～76	M：F＝2：1	1例は体部大弯中心，巨大皺襞様	粘膜固有層・下層	3/3	早期	IIa, IIc, IIa＋IIc
小田ら[9]	1	54	M	体部大弯中心，巨大皺襞形成	粘膜固有層・下層	あり	早期	陥凹型
自験例	1	66	M	体部大弯，巨大皺襞形成	粘膜固有層・下層	あり	進行	粘膜腫瘍型
	合計 18	平均 60.4	男女比 12：6			8/18 例		

Table 3. DCM とびまん性粘膜下異所性胃腺の共通点と相違点

共通点
1. 胃壁内の多発嚢胞病変
2. 嚢胞周囲の平滑筋線維の増生
3. 巨大皺襞症を呈することがある
4. 高頻度に胃癌を合併する

相違点	DCM	びまん性粘膜下異所性胃腺
1. 胃壁肥厚	広範囲	必須でない
2. 嚢胞の局在	粘膜固有層かつ/または粘膜下層	粘膜下層
3. 背景胃粘膜	萎縮・腸上皮化生なし	萎縮・腸上皮化生あり
4. 原因	先天性	繰り返す炎症

嚢胞性異所を有する疾患は岩永[5]により 28 例，米村[6]により 10 例が，それぞれびまん性胃粘膜下異所腺，多発性胃粘膜下嚢腫として報告されている．

DCM とびまん性粘膜下異所性胃腺は，これまでの多くの報告ではほぼ一致する病態として考察されているが[5)~8)10)11)]相違点も指摘されている[9]．過去の報告から抽出した共通点と相違点を Table 3 に整理した．共通点の 1 点目は胃壁内の多発嚢胞性変化である．EUS で第 2 層ないし 3 層の多発嚢胞病変と肥厚としてとらえられることが多いが[7)~9)]，本例においては術前に多発嚢胞が壁肥厚の一因であることが認識できなかった．その理由として比較的嚢胞の直径が小さかったことが考えられる．Hizawa ら[7]は，病理学的検索に比べて EUS で嚢胞病変が確認できる頻度が低い要因として 1mm 以下の嚢胞病変に対する EUS の分解能の限界を指摘している．

2 点目の共通点は嚢胞周囲に平滑筋線維の増生が見られることである[1)~6)9)]．本例においては α-SMA 染色によりそれを確認した（Figure 7a, b）が，免疫染色により証明したものは過去になかった．また今回著明な体部大弯の胃壁肥厚の要因として，HE 染色で間質の線維性増生が見られたため特殊染色を行い，浅層の弾性線維と深層の膠原線維の増生を確認した．多発嚢胞を含むそれらの

線維性増生が，肥厚した第2層の低エコー像としてEUSでとらえられたものと思われた．過去に間質の線維性増生に関して検討した報告はなく，今後の症例蓄積によりその原因や疾患特異性を明らかにしたい．

3点目の共通点は，まれに巨大皺襞症を呈することである．胃巨大皺襞症とはX線二重造影で皺襞幅が10mm以上と定義され[2]，鑑別診断として4型進行癌，悪性リンパ腫，肥厚性胃炎，メネトリエ病，DCMが挙げられる．超音波内視鏡はその診断に有用で[3][14]，4型進行癌では第3層および第4層の著明な肥厚が見られ，悪性リンパ腫では層構造の消失した低エコー像が特徴である．肥厚性胃炎では第1，2層の肥厚が見られ，しばしば粘膜固有層深部に嚢胞状拡張腺管が見られる[9]．本例では超音波内視鏡検査で第2層に小嚢胞をともなう肥厚が見られたが，粘膜固有層の腺管拡張として矛盾のない所見と判断したため肥厚性胃炎として経過観察した．医学中央雑誌とMEDLINEにて巨大皺襞症（giant fold），diffuse cystic malformationをキーワードとして検索し得た範囲で，国内に2例の巨大皺襞症を呈するDCM報告が見られた[8][9]．一方奥脇ら[10]は，粘膜下異所性胃腺の本邦報告47例中6例を巨大皺襞型に分類している．よって巨大皺襞症の鑑別診断としてまれではあるがDCMを考慮する必要がある．

共通点として最後に，高頻度に胃癌を合併することが挙げられる．Table 2に示すように本例を含めた過去の報告においてDCM 18例中8例で胃癌の合併が報告されている[4][7]~[9]．びまん性粘膜下異所性胃腺もまた高頻度に胃癌にともなう病変，つまりpara-cancerous lesionとして認識されており，さらに多発胃癌の頻度も高いとされる[5]．胃癌非合併例においては将来発癌の可能性が危惧され慎重な経過観察が必要と考えるが，経過観察中に発癌を確認したのは自験例のみであった．

本例は表面粘膜から発生する通常の胃癌ではなく，粘膜面に癌の露出を認めない粘膜下腫瘍様進行胃癌を発症した．腫瘍周囲に多発嚢胞を認めたことから，嚢胞上皮自体の発癌，つまりprecancerous lesion（前癌病変）としてのDCMからの発癌というまれな病態が考えられた．粘膜下腫瘍様胃癌は全胃癌の0.1~1.3%と低頻度で，粘膜下異所腺組織からの発生が原因のひとつに挙げられている[1][15]．粘膜面への癌細胞の露出が少ないため通常の鉗子生検では診断が困難なことが多く，EUS-FNAによる診断の有用性が報告されている[15]．医中誌とMEDLINEにてdiffuse cystic malformation，異所性胃腺（heterotopic gastric mucosa），粘膜下腫瘍（submucosal tumor），胃癌（gastric cancer）をキーワードとして検索し得た範囲で，DCMと粘膜下腫瘍様胃癌の合併は早期癌1例が報告されている[1]のみであった．

相違点の1点目として，DCMでは広範囲の胃壁肥厚が特徴とされ[1]~[4][7][8]，本例もその特徴を備えていた．

相違点の2点目は，多発嚢胞病変の存在する層が異なることである．DCMでは粘膜下層のみならず粘膜固有層にも嚢胞が見られるのに対し[1]~[4][7][9]，びまん性粘膜下異所性胃腺では全例粘膜下層に見られる[5][6]．先述のように自験例においては粘膜筋板の走行は不明となり粘膜固有層と粘膜下層の区別ができない状態であったが，本来粘膜固有層に相当すると推定される表層にも多発嚢胞が認められた（Figure 7）．

相違点の3点目は，DCMが萎縮や腸上皮化生のない胃に認められるのに対して，びまん性粘膜下異所性胃腺は背景粘膜に例外なく高度の萎縮性変化をともなうことである[5][6]．過去の報告において両疾患の相違点に関する議論は少ないが，小田ら[9]は嚢胞病変が中村らのいうF境界線（腸上皮化生のない胃底腺粘膜領域を境界づける線[16][17]）の口側，つまり腸上皮化成のない粘膜下に分布することをDCMであることの根拠のひとつとして挙げている．自験例においても嚢胞病変は萎縮や腸上皮化生のない粘膜内部に存在し，DCMに合致する所見であった．

相違点の4点目は推定される成因が異なることである．DCMは先天的に腺組織が粘膜下層に迷入する発育異常であるとする先天性迷入説が有力

である[10]のに対して，びまん性粘膜下異所性胃腺は繰り返される粘膜の炎症と再生がその発生要因とする後天性説が支持されている[6]．胃粘膜萎縮や腸上皮化成は粘膜の炎症，再生の結果とされる．

結　語

巨大皺襞症を呈し10年間の経過観察中に粘膜下腫瘍様進行胃癌を発症したDCMの1例を報告し，びまん性粘膜下異所性胃腺との異同について整理した．通常内視鏡によるフォローアップのみでは粘膜下腫瘍様胃癌を早い段階で指摘することは困難で，診断が遅れ致命的となる可能性が示唆された．胃巨大皺襞症の鑑別診断としてDCMを念頭に置き，EUSでの慎重な定期的フォローアップと粘膜下腫瘍が認められた際に積極的なEUS-FNA施行による病理診断が望ましいと思われた．

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本論文内容に関連する著者の利益相反
：なし

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A case of diffuse cystic malformation in which submucosal tumor-like advanced gastric cancer was identified during 10-year follow-up

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A 66-year-old man with giant gastric folds had been followed up since February 2000. In March 2010, a submucosal tumor of 35mm was identified with endoscopy and a low echoic mass was identified with endoscopic ultrasonography. After histologic diagnosis by endosonography-guided fine needle aspiration biopsy, he underwent a total gastrectomy. Histologic examination of the resected specimen revealed a tumor 20mm in diameter consisting of well-to-moderately differentiated tubular adenocarcinoma in the thickened wall of the gastric greater curvature, which contained small cystic lesions in the lamina propria. Immunohistochemical staining showed thick gastric wall consisting of not only multiple cysts but also smooth muscle, elastic and collagen fibers. The histologic diagnosis was advanced gastric cancer accompanied by diffuse cystic malformation (DCM). Although it is a rare condition, DCM should be considered in the differential diagnosis of giant gastric folds and as a pre-cancerous lesion.

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Guidelines for Indication and Management of Pregnancy and Delivery in Women With Heart Disease (JCS 2010)

– Digest Version –

JCS Joint Working Group

Table of Contents

(*Circ J* 2012; **76:** 240–260)

I Introduction to the Revised Guidelines

The latest version of the guidelines includes new findings of papers published after publication of the previous version[1] to reflect the current practice. Some sections regarding obstetrics and specific diseases were revised significantly, while other sections are kept almost unchanged because few reports have been published after publication of previous version. The current guidelines include new sections of "psychosocial issues" (subsection of the "Pre-Pregnancy Counseling"), "Hemodynamic Assessment During Pregnancy", "Drug Therapy During Pregnancy" and "Directions of Future Research".

II General Description

1. Cardiovascular Change During Pregnancy and Delivery

Hemodynamics during pregnancy and delivery is significantly affected by changes in fluid circulation, hematology, respiratory function, endocrinology and the autonomic nervous system.[2,3] Plasma volume begins to increase from 4 weeks of gestation, peaks at 32 weeks of gestation, and then is maintained at a similar level or increase gradually to the volume 40 to 50%

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higher than that before pregnancy.[4–7] Heart rate peaks at around 32 weeks of gestation to about 20% higher than that before pregnancy. Cardiac output increases to 30 to 50% higher than that before pregnancy at 20 to 24 weeks of gestation, and is maintained at a similar level throughout the pregnancy.[6,7] Aortic pressure and systemic vascular resistance decrease during pregnancy. Uterine contraction and labor pain causes increases in circulatory volume by 300 to 500 ml, cardiac output by 15 to 25% and heart rate and blood pressure.[2,3] It is preferable that women in labor be kept in the left decubitus. Typical blood loss during vaginal delivery is about 500 ml, while that during cesarean section is about 1,000 ml. Immediately after delivery, venous return increases abruptly after the pressure on the inferior vena cava from the growing uterus was relieved. It takes about 4 to 6 weeks to return to a normal hemodynamic status after delivery.[2,3] During the first and second trimesters, hemoglobin and hematocrit levels decrease, which causes a relative anemia.[8–10] The risk of thromboembolism increases during pregnancy. Since aortic wall becomes fragile during pregnancy, aortic dissection may occur in susceptible patients such as Marfan syndrome associated with dilated aorta.

2. Cardiac Assessment Before Pregnancy

It is important for women with heart diseases to undergo appropriate assessment of pulmonary artery pressure, ventricular function, aortic diameter, cyanosis, New York Heart Association (NYHA) classification and other appropriate items to predict the risk of pregnancy-related complications in mother and fetus. Pre-pregnancy checkup for patients with underlying heart diseases includes history taking, physical examination, chest X-ray, electrocardiogram (ECG) and echocardiography. Cardiac catheterization, exercise stress test[11] and Holter monitoring may be also conducted whenever necessary.

3. Pre-Pregnancy Counseling

Women with heart diseases should receive pre-pregnancy counseling, including discussion about the risk to the mother, risk to the fetus, hereditary risk, possible course of pregnancy, and sexual activity and caring for baby. The prevalences of menstruation disorders and amenorrhea are high among women with a history of congenital heart disease especially those with a history of cyanotic congenital heart disease and those who underwent multiple surgeries. Frequent menstrual disorders and poor fertility are common findings among women with residual cyanosis following Fontan operation,[12,13] and women with cyanotic congenital heart disease. Recurrence rate of heart disease is higher in patients with congenital heart disease than in healthy parents, and the incidence is higher in children of mothers with congenital heart disease than those of fathers with it. It is likely that women with heart disease experience heart failure and/or arrhythmia after delivery, and encounter difficulties in caring for baby due to poor cardiac function.[14,15] Patients with heart disease often cannot have life insurances.[16–18] Although the NYHA classification is often used to consider whether pregnancy is contraindicated or not, physicians must not rely solely on it to predict the prognosis of pregnancy of their individual patients. Table 1 lists patients with heart diseases and conditions that require careful monitoring during pregnancy or should be advised to avoid pregnancy.

Permanent sterilization procedures include tubal ligation, and temporal sterilization procedures include intrauterine devices, low-dose birth control pills, and the classic barrier method. Male contraceptive methods include permanent methods via vasoligation and temporary methods using condoms.

Table 1. Patients With Heart Diseases Requiring Careful Monitoring During Pregnancy or Strongly Recommended to Avoid Pregnancy

- Pulmonary hypertension (Eisenmenger syndrome)
- Outflow tract stenosis (severe aortic stenosis with a mean pressure gradient of >40 to 50 mmHg)
- Heart failure (NYHA Class III to IV, left ventricular ejection fraction <35 to 40%)
- Marfan syndrome (ascending aortic diameter at end-diastole >40 mm)
- Mechanical valves
- Cyanotic heart disease (arterial oxygen saturation <85%)

NYHA, New York Heart Association.

Patients with heart disease must be educated about genetics such as the risk of familial recurrence of heart disease. The Guidelines for Genetic Test and Genetic Counseling in Cardiovascular Disease proposed by the Japanese Circulation Society (JCS) in 2006 describe how to provide genetic counseling for patients with heart disease in detail.[19] Congenital cardiovascular diseases, which are known to occur in 1.06% among liveborn infants in Japan, are the most common congenital disorders to cause neonatal death.[20] They are reported to be accounted for genetic factors (about 12.9%) including chromosomal abnormalities (eg, Down syndrome, Turner syndrome, 22q11.2 deletion syndrome and Williams syndrome, 8.2%) and genetic disease (eg, Noonan syndrome, Holt-Oram syndrome, Marfan syndrome, Jervell-Lange-Nielsen syndrome, 4.7%); disorders involving environmental (external) factors (0.5%) such as those affected by mother's systemic disease, fetal infections and teratogens; and disorders of unknown cause involving multifactorial inheritance (86.7%) (eg, many of congenital heart diseases, idiopathic pulmonary hypertension and idiopathic cardiomyopathy) (Table 2).[21] Congenital heart diseases may be caused by not only genetic abnormalities but also environmental factors possibly affecting fetuses and mothers during pregnancy.

Psychosocial issues are also important during pregnancy and delivery. Anxiety and depression may worsen during the perinatal period.[22] Patients with heart disease have strong desire to experience pregnancy and having a baby, and often feel anxiety about the possible effect of pregnancy on their health and potential genetic risks to the child. In order to prevent depression and anxiety during the perinatal period, patients should be provided with correct information and education on heart disease, contraception, sexual activity and social support during the period of adolescence.[23]

4. Cardiac Monitoring of the Mother During Pregnancy

In women with heart disease, complications during pregnancy may often develop in the mother and fetus, and may sometimes be fatal. They must be continuously monitored by a team consisting of obstetricians, cardiologists, anesthesiologists, and nurses for arrhythmia, heart failure and thrombosis during pregnancy.[24] Periodic checkups for healthy pregnant women generally consist of 3 checkups by 11 weeks of gestation, every 4 week monitoring in 12 to 23 weeks of gestation, every other week monitoring in 24 to 35 weeks of gestation,

Table 2. Congenital Cardiovascular Diseases Due to Inherited Abnormalities or Chromosomal Aberrations

Diagnosis	Cardiovascular findings	Non-cardiovascular findings	Causative gene mutation or variant protein	Gene locus
Alagille syndrome	Peripheral pulmonary stenosis, pulmonary valve stenosis, tetralogy of Fallot, ventricular septal defect, atrial septal defect, aortic stenosis, coarctation of the aorta	Cholestasis, specific facial appearance, mental retardation, renal dysplasia, eye abnormalities, butterfly vertebrae	*JAG1(jagged-1)* *NOTCH2*	20p12 1p12
Barth syndrome	Dilated cardiomyopathy, left ventricular noncompaction	Neuromuscular disorders, leukopenia, mitochondrial metabolic disorders, mental retardation	*TAZ (Tafazzin)*	Xq28
Cat eye syndrome	Hypoplastic left heart, total anomalous pulmonary venous drainage, ventricular septal defect, atrial septal defect	Iris tear, anal atresia, malformed ears, small jaw, renal malformation	*DGCR*	Duplication 22q11.1
CHARGE association	Tetralogy of Fallot, atrioventricular septal defect, Ebstein's anomaly, complete transposition of the great arteries	Coloboma, choanal atresia, developmental retardation, renal malformation, genital hypoplasia, malformed ears, hearing loss, tracheoesophageal fistula	*CHD7* *SEMA3E*	8q12.1 7q21.11
Down syndrome	Atrioventricular septal defect, ventricular septal defect, atrial septal defect, aberrant subclavian artery	Specific facial appearance, growth/developmental retardation, duodenal atresia, anal atresia, tracheomalacia, hearing loss, hypothyroidism, muscular hypotonia, leukemia	Multiple	Trisomy 21
Duchenne muscular dystrophy	Cardiomyopathy, conduction disorder, mitral valve prolapse	Progressive skeletal muscle atrophy	*DMD (Dystrophin)*	Xp21.2
Edward syndrome	Ventricular septal defect, patent ductus arteriosus, bicuspid aortic valve, bicuspid pulmonary valve	Intrauterine growth retardation, polyhydramnios, umbilical vessel anomalies, specific facial appearance, psychomotor retardation, overlapping fingers, muscular hypotonia	Multiple	Trisomy 18
Ehlers-Danlos syndrome	Mitral valve prolapse, tricuspid valve prolapse, aortic dilatation, cerebral aneurysms, atrial septal defect	Fragile skin, joint/skin hyperextensibility, subcutaneous bleeding, blue sclera, pneumothorax	*COL5A1,A2* (Types I and II), *COL3A1* (Type IV), *PLOD* (Type IV)	9q34.2-q34.3 2q31 1p36.3
Ellis-van Creveld syndrome	Large atrial septal defect, atrioventricular septal defect	Short extremities, polydactyly, nail hypoplasia, pelvic dysplasia	*EVC*	4p16
Fabry disease	Myocardial ischemia, myocardial infarction, mitral regurgitation, left ventricular hypertrophy, cardiomyopathy, arrhythmia, congestive heart failure	Extremity pain, paresthesia, angiokeratoma, hypohidrosis, renal failure, cerebrovascular disorders, corneal opacity, cataract, constipation, esophageal achalasia, hearing loss	*GAL (Alpha-galactosidase)*	Xq22.1
Friedreich ataxia	Cardiomyopathy, conduction disorder	Progressive ataxia, muscular hypotonia	*FRDA (Frataxin)*	9q13
Goldenhar syndrome	Ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, atrial septal defect	Asymmetrical facial features, spinal anomalies, microtia, mandibular hypoplasia, hearing loss, conjunctival epidermoid carcinoma	Unknown	Unknown
Heterotaxy syndrome	Single atrium, single ventricle, common atrioventricular canal, pulmonary atresia, transposition of the great arteries, atrioventricular septal defect, conduction disorder	Kartagener syndrome: male infertility, heterotaxia, bronchoectasis, hearing loss Ivemark syndrome: asplenia/polysplenia	*ZIC3, LEFTY2, CFC1, ACVR2B*	Xq26.2 3p22-p21.3 1q42.1 2q21.1
Holt-Oram syndrome	Atrial septal defect, ventricular septal defect, conduction disorder (sinus bradycardia, atrioventricular block)	Radial anomaly (thumb anomalies, 2nd to 5th finger anomalies), upper limb hypoplasia	*TBX5*	12q24.1
Homocystineuria	Thromboembolism, aortic dilatation	Congenital metabolic disorders, mental retardation, skeletal anomalies (tall stature, extension of fingers and toes), ectopia lentis, psychiatric disorder, osteoporosis	*MTHFR*	1p36.3

(Table 2 continued next page.)

Diagnosis	Cardiovascular findings	Non-cardiovascular findings	Causative gene mutation or variant protein	Gene locus
Hurler syndrome	Cardiomyopathy, atrioventricular and semilunar valve insufficiency	Congenital metabolic disorders, specific facial appearance, progressive osteodysplasty, developmental retardation, corneal opacity, hearing loss, growth disorder, scoliosis, hypertrichosis, splenohepatomegaly	*IDUA (Alpha-L-Iduronidase)*	4p16.3
Jacobsen syndrome	Hypoplastic left heart, atrial septal defect, ventricular septal defect	Psychomotor retardation, specific facial appearance, deformed toe joints (hammer toe syndrome)	*BARX2*	Deletion 11q25
Jervell-Lange-Nielsen syndrome	Long QT syndrome	Hearing loss	*KCNQ1* *KCNE1*	11p15.5 21q22.1-q22.2
Kabuki make up syndrome	Coarctation of the aorta, bicuspid aortic valve, mitral valve prolapse, ventricular septal defect, pulmonary artery stenosis, aortic stenosis, mitral stenosis, tetralogy of Fallot, single ventricle, double outlet right ventricle, malposition of the great arteries	Specific facial appearance, psychomotor retardation, dermatoglyphic abnormalities, skeletal anomalies (scoliosis, hip dysplasia, shortened 5th finger), hearing loss	Unknown	Sporadic
LEOPARD syndrome	Pulmonary artery stenosis, atrioventricular block, hypertrophic cardiomyopathy	Multiple lentiginosis, ocular hypertelorism, external genitalia abnormalities, mental retardation, developmental disorder, hearing loss	*PTPN11, KRAS, SOS1, RAF1*	12q24.1 12p12.1 2p22-p21 3p25
Marfan syndrome	Aortic dilatation, atrioventricular valve regurgitation, mitral valve prolapse, annuloaortic ectasia, dissecting aortic aneurysm, pulmonary artery dilatation, pulmonary regurgitation	Tall stature, lens dislocation, myopia, blue sclera, scoliosis, funnel chest, spider-like fingers, joint hyperextensibility, long extremities	*FBN1 (Fibrillin)* *TGFBR1,2*	15q21.1 9q33-q34 3p24.1
Leigh encephalopathy, NARP syndrome	Hypertrophic cardiomyopathy	Progressive psychomotor developmental disorder, convulsions, cerebellar ataxia, feeding and swallowing disorder, muscular hypotonia, optic atrophy	*Mitochondrial loci*	Mitochondrial DNA
MERRF syndrome	Cardiomyopathy	Myoclonus, epilepsy, cerebellar ataxia, muscular hypotonia, intellectual deterioration, short stature	*MTTK*	Mitochondrial DNA
Myotonic dystrophy	Conduction disorder, cardiomyopathy, mitral regurgitation	Myotonia, muscle degeneration, cataract, blepharoptosis	*DMPK , ZNF9*	19q13.2 3q13.3
Noonan syndrome	Pulmonary artery stenosis, hypertrophic cardiomyopathy, atrial septal defect	Webbed neck, short stature, developmental retardation, pectus carinatum, funnel chest, blepharoptosis, bleeding tendency, abnormal platelet function	*PTPN11, KRAS, SOS1, RAF1*	12q24.1 12p12.1 2p22-p21 3p25
Osteogenesis imperfecta	Mitral valve prolapse, aortic regurgitation, aortic dilatation	Fragile bones, frequent bone fractures, hearing loss, blue sclera, short bowing legs, growth disorder, specific facial appearance	*COL1A1* *COL1A2*	17q21.33 7q21.3
Trisomy 13	Ventricular septal defect, patent ductus arteriosus, atrial septal defect	Mental retardation, holoprosencephaly, microcephaly, sloping forehead, hearing loss, malformed ears, rocker bottom feet, polydactyly	Multiple	Trisomy 13
Pompe disease	Myocardial hypertrophy due to glycogen storage	Congenital metabolic disorder, muscular weakness, hepatomegaly, macroglossia	*GAA (Lysosomal Alpha-Glucosidase)*	17q25
Rubinstein-Taybi syndrome	Various congenital heart diseases, hypoplastic left heart	Developmental disorder, specific facial appearance, hypertrichosis, drooping eyelid, ocular hypertelorism, maxillary hypoplasia, forehead enlargement, short stature, broad thumb-hallux	*CREBBP (CREB binding protein)*	16p13.3
Treacher-Collins syndrome	Ventricular septal defect, patent ductus arteriosus, atrial septal defect	Malformed ears, hearing loss, mandibular hypoplasia, cheek bone hypoplasia, choroidal coloboma, bilateral lower eyelid coloboma, cleft palate, choanal atresia	*TCOF1 (Treacle protein)*	5q32

(Table 2 continued next page.)

Diagnosis	Cardiovascular findings	Non-cardiovascular findings	Causative gene mutation or variant protein	Gene locus
Tuberous sclerosis	Cardiac tumor (rhabdomyoma), arrhythmia	Tumors, convulsions, facial angiofibromas, leukoderma, cafe-au-lait spots, osteosclerosis, renal hypoplasia, mental retardation, autism	*TSC1 (Hamartin), TSC2 (Tuberin)*	9q34 16p13.3
Turner syndrome	Coarctation of the aorta, bicuspid aortic valve, hypoplastic left heart, atrial septal defect, ventricular septal defect	Short stature, webbed neck, shield chest, low hairline, ovarian hypoplasia, renal hypoplasia, hearing loss	Multiple	Monosomy X (45, X)
VACTERL syndrome	Ventricular septal defect, atrial septal defect, patent ductus arteriosus	Spinal anomalies, anal atresia, tracheo-oesophageal fistula, radial dysplasia, limb anomalies, renal/urinary anomalies	*Numerous loci*	Unknown
22q11.2 deletion syndrome	Interruption of the aorta, persistent truncus arteriosus, tetralogy of Fallot with pulmonary atresia, right aortic arch, aberrant subclavian artery, ventricular septal defect	Conotruncal anomaly face, cleft palate with nasopharyngeal insufficiency, thymus hypoplasia, hypoparathyroidism, hypocalcemia, increased infection susceptibility, anal atresia, mental retardation, psychiatric disorders, thrombocytopenia	*TBX1 , UFD1L*	del 22q11.2
Williams syndrome	Supraaortic stenosis, supra-valvular pulmonary stenosis, peripheral pulmonary artery stenosis, aortic stenosis, pulmonary artery stenosis, cardiomyopathy	Mental retardation, elfin face, stellate pattern in iris, hypercalcemia, malocclusion, visuospatial cognitive disorders, joint contracture, hypertonia, learning disorder, cognitive visual impairment	*ELN (Elastin)*	7q11.23

and weekly thereafter to the end of the 40th week. For women with heart disease, an appropriate monitoring schedule should be designed on the basis of healthy pregnant women according to the risk during pregnancy. When women with heart disease become pregnant, attending cardiologists must explain the condition of heart disease to obstetricians, and provide information on important points to be monitored during pregnancy and the perinatal period.

5. Hemodynamic Assessment During Pregnancy

It is preferable that patients with heart disease be assessed for hemodynamic status several times during pregnancy and the puerperal period. Echocardiography, a noninvasive method providing detailed information, is very useful in evaluating hemodynamics during pregnancy.[25] The first assessment should be conducted immediately before pregnancy or during the first trimester when changes in hemodynamics are still slight. Patients with mild to moderate risk should be evaluated for hemodynamics again during the late second trimester (26 to 28 weeks of gestation).[26] Patients with severe risk require more frequent hemodynamics assessment. During the peripartum period, hemodynamics should be reassessed. Since child care including breast feeding may increase cardiac load, patients with severe heart disease must be followed up for at least 6 months after childbirth for clinical course including hemodynamics. Although cardiac MRI is believed useful for assessing right heart function and patients with complex congenital heart disease, this technique must be limited for necessary cases since the risk to the fetus remains unclear.[27] Cardiac catheterization and cardiac CT should be limited to patients who may benefit from the examination as these techniques cause radiation exposure. Since no increases in the risks of developmental retardation, central nervous system disorders and developmental disorders have been observed in children exposed to less than 100 mGy, exposure to radiation at this level is not considered to a valid reason for artificial termination of pregnancy.[28]

6. Fetal Examination

The fetal well-being can be assessed using fetal heart rate monitoring[29–31] and ultrasonic methods such as ultrasonic tomography and Doppler sonography.[32,33] Fetal heart rate monitoring is performed using nonstress tests (NST) or contraction stress tests (CST) to evaluate the fetal well-being and the fetal reserve. In the ultrasonic tomography, the biophysical profile (BPP) and a modified BPP combining a NST and an amniotic fluid index are used. Doppler sonographic assessment of fetal hemodynamics is performed on the basis of the systolic to diastolic (S/D) ratio, resistance index, and/or pulsatility index, which represent the vascular resistance in the peripheral vascular beds. The false positive rate is high in fetal assessment methods: The incidences of fetal death among fetuses determined to be in good condition in the NST, CST and BPP have been reported to be 1.9 to 6.45%, 0.3% and 0.65%, respectively.[32]

The presence of heart disease in either parent should be considered to represent a high risk for congenital heart disease in the fetus, and screening using fetal echocardiography should be indicated. In Japan, artificial termination of pregnancy is allowed by 22 weeks of gestation. Since assessment for fetal heart disease to be conducted by 22 weeks of gestation may provide important information for whether the pregnancy should be continued or not, physicians must fully explain the meaning of the assessment to the parents and obtain their informed consent. Fetal heart screening is possible at 18 weeks of gestation and thereafter, and fetal heart condition is best assessed in 20 to 24 weeks of gestation. Since heart anomaly may be first found in the third trimester, it is preferable that the fetal heart condition be assessed again in 30 weeks of gestation or thereafter.

7. Infective Endocarditis

The Guidelines for the Prevention and Treatment of Infective Endocarditis published by the JCS in 2008[34] recommend that the prevention of infective endocarditis be considered for most patients with congenital heart diseases. The most common sources of bacteremia are urogenital infection, delivery, childbirth, indwelling catheter and surgeries. Bacteremia may develop after spontaneous abortion, vaginal delivery assisted by episiotomy or cesarean section, among others. Antibiotic treatment of infective endocarditis should be performed in a fashion similar to that for non-pregnant patients according to the susceptibility of causative agents.[35]

Preventive administration of antimicrobial agents during delivery is recommended for patients with a high risk for infective endocarditis (**Table 3**).[36–38] Although preventive administration of antimicrobial agents is not recommended for patients in whom the risk for infective endocarditis is not high because of its low incidence, the benefits of preventive antimicrobial treatment are not denied considering the risk-benefit balance. There are no currently available guidelines for the preventive administration of antimicrobial agents during delivery. **Table 4** lists common measures to prevent infective endocarditis associated with urogenital or gastrointestinal surgeries/procedures.[39]

Table 3. Patients With Heart Diseases Recommended to Receive Preventive Antimicrobial Treatment During Obstetric Operations/Procedures and Delivery

- Patients with a history of infective endocarditis
- Patients with congenital heart disease
  - Patients with cyanotic heart disease
  - Patients who underwent complete repair using artificial patches and devices within the last 6 months
  - Patients who underwent repair and have remaining shunts around the implanted artificial patches and devices
- Patients using artificial valves
- Patients after heart transplant (receiving immunosuppressants or having valvular heart disease)

8. Drug Therapy During Pregnancy

Drugs used for pregnant women must be selected after careful consideration of the risk-benefit balance in the mother and fetus. The adverse effects of drugs on fetuses are classified into teratogenic effects and fetal toxicity. Since many drugs are not substantially excreted in the breast milk of nursing mothers, the blood concentration of a drug given to the nursing mother is substantially lower than the therapeutic range of the drug in the neonate. The pregnancy category proposed by the Food and Drug Administration (FDA) of the United States is often referred to as important information on the risk of drugs to the fetus or neonate.[40] When drugs contraindicated for pregnant women in the package inserts or drugs not accepted by the National Health Insurance (NHI) are used, the physicians must fully explain the risks and benefits of such drugs to the patients and their families and obtain informed consent.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated for women in the second and third trimester since they may directly affect the kidney of the fetus and neonate to cause renal failure, abortion or stillbirth.[41,42] Amiodarone is basically contraindicated for pregnant women since it may cause abnormal thyroid function in the fetus. Bosentan is absolutely contraindicated for pregnant women in the FDA's recommendation. Warfarin is teratogenic when given during the first trimester, and increases the risk for bleeding disorders in the fetus and neonate. Heparin does not have fetal toxicity because it does not cross the placenta, while the incidence of thrombosis among patients receiving heparin is higher than those receiving warfarin. Low-dose aspirin therapy is rated pregnancy category C by the FDA's recommendation and believed relatively safe. However, "aspirin is contraindicated for women in the last 12 weeks of gestation (regardless of the dose)" in the package insert; physicians must fully explain the risks and benefits of aspirin therapy during the second and third trimester of pregnancy to obtain consent from the patient.

9. Care Facility for Pregnancy

Women with heart disease in whom pregnancy poses a risk must be carefully monitored and planned for safer pregnancy and childbirth. High-risk pregnancy should be monitored in tertiary care facility in which team approach by obstetricians, heart disease specialists (eg, cardiologists, pediatric cardiologists, specialists of congenital heart disease in adults, and cardiovascular surgeons), anesthesiologists and neonatologists who have knowledge and experience in the management of high-risk pregnancy has been established. Every tertiary care

Table 4. Prevention of Infective Endocarditis in Patients Receiving Urogenital or Gastrointestinal Surgery/Procedures

Patients	Treatment
• For patients with heart disease in whom serious endocarditis may occur	
Patients who are not allergic to ampicillin/amoxicillin	Administer ampicillin 2.0 g and gentamycin 1.5 mg/kg (maximum dose 120 mg) intramuscularly or intravenously ≤30 minutes before delivery. Administer intravenous ampicillin 1.0 g or oral amoxicillin 1.0 g 6 hrs after delivery.
Patients who are allergic to ampicillin/amoxicillin	Administer intravenous vancomycin 1.0 g (infuse over 1 to 2 hrs) and intramuscular or intravenous gentamycin 1.5 mg/kg (maximum dose 120 mg) to conclude administration ≤30 minutes before delivery
• For other patients	
Patients who can take drugs orally	Administer oral amoxicillin 2.0 g (at lower doses for small patients) 1 hour before delivery
Patients who cannot take drugs orally	Administer intravenous or intramuscular ampicillin 2.0 g ≤30 minutes before delivery
Patients who are allergic to ampicillin/amoxicillin	Administer intravenous vancomycin 1.0 g (infuse over 1 to 2 hrs) to conclude administration ≤30 minutes before delivery

Cited from *Circ J* 2003; **67**(Suppl IV): 1039–1082.[39]

facility in which pregnancy and childbirth in patients with heart disease are managed should establish such a specialist team. Hospitals where such team cannot be established within the institutions should build a system to facilitate consultation with heart disease specialists in other hospitals.

III Specific Maternal Conditions

1. Congenital Heart Disease

Patients with atrial septal defect do not have a high risk for cardiac complications during pregnancy and childbirth, but do has a higher risk for fetal/neonatal complications.[43,44] Patients with ventricular septal defect who had not had signs/symptoms of heart failure during childhood but have only a small left-to-right shunt in adulthood may well tolerate pregnancy and childbirth well. Patients with endocardial cushion defect (atrioventricular septal defect) may often go through the process of pregnancy and childbirth without significant problems, but management of atrial arrhythmia may become necessary in some cases. Patients with patent ductus arteriosus may go through the process of pregnancy and childbirth without significant problems if the shunt volume is small and pulmonary arterial pressure is normal.[45] Patients with mild to moderate congenital aortic stenosis will be free from complications throughout pregnancy. However, in patients with severe aortic stenosis the aortic pressure gradient may increase as the pregnancy progresses, and may pose a risk to the mother. It is recommended that patients with severe aortic stenosis undergo aortic valve replacement or balloon aortic valvuloplasty to treat aortic stenosis before pregnancy.[46–48] Since mechanical valve replacement will require anticoagulation therapy which may pose a risk for the mother and fetus (See the section of "Valvular Heart Diseases"), having bioprosthetic valve replacement or Ross operation other than mechanical valve are recommended for women who want to become pregnant in future. Bicuspid aortic stenosis may lead to aortic dissection. The prognosis of pregnancy in patients with pulmonary stenosis is generally preferable, but percutaneous balloon pulmonic valvuloplasty should be considered for symptomatic patients with severe stenosis.[49] Although patients with a mild case of Ebstein's anomaly will rarely experience pregnancy complications, patients with a severe case of it may experience right heart failure, paradoxical thromboembolism, infective endocarditis, hypoxemia or other complications.[50] The risk of complications in the mother and fetus is small among patients with corrected transposition of the great arteries when their intracardiac abnormalities are mild, although the progression of systemic right ventricular dysfunction and tricuspid regurgitation (systemic atrioventricular valve regurgitation) may occur in some cases.[51,52]

In patients with acyanotic heart disease after repair with mild residua and sequelae, pregnancy, childbirth and vaginal delivery are feasible.[45,53,54] It is recommended that patients who have moderate to severe residua and sequelae which may worsen during pregnancy be treated with re-operation, catheter intervention or other appropriate measures to repair that before pregnancy.

Since repair is successful in many patients with tetralogy of Fallot, the risks for pregnancy and childbirth in them are similar to those observed in healthy pregnant women.[55] The presence of right ventricular dysfunction due to severe pulmonary regurgitation, left ventricular dysfunction or pulmonary hypertension increase the risk during pregnancy and childbirth, and may worsen heart failure or cause tachyarrhythmia. The risk to the fetus is relatively high, and the incidence of spontaneous abortion is higher in patients with tetralogy of Fallot after repair than in healthy pregnant women.[56–60] It is recommended that patients with severe right ventricular outflow tract stenosis undergo reoperation before pregnancy.

Patients following Fontan operation with a NYHA classification of I to II, favorable cardiac function, and sinus rhythm may tolerate cardiac load during pregnancy and can thus complete pregnancy and childbirth, but the number of such patients is not large (**Table 5**).[12,61,62]

The risk during pregnancy is not high among patients with complete transposition of the great arteries who underwent atrial switch operation (eg, Mustard operation or Senning operation), have favorable systemic ventricular function and only mild residua. The incidences of spontaneous abortion and obstetric complications are high. The prevalences of premature birth and low birth weight infants are high. Heart failure, right ventricular dysfunction, worsening of tricuspid regurgitation or supraventricular tachycardia including atrial fibrillation may also occur.[63–66] Although cardiac function is generally good and the incidence of arrhythmia is relatively low in patients following arterial switch operation (Jatene procedure), the presence of pulmonary stenosis, pulmonary regurgitation, aortic regurgitation or ischemic lesions due to coronary stenosis/occlusion increases the risk of complications in these patients.[67] Although few cases have been reported on pregnancy and childbirth in patients following Rastelli operation, the risk during pregnancy and childbirth is not high among patients with good cardiac function and without severe stenosis of right ventricular outflow tract.[68] Since patients with severe stenosis of right ventricular outflow tract are highly likely to have right ventricular dysfunction, ventricular tachycardia or supraventricular tachycardia including atrial fibrillation, it is recommended that they undergo reoperation to treat the stenosis before pregnancy.[69]

Patients who have cyanosis and patients with Eisenmenger syndrome have an extremely high risk to the mother and fetus during pregnancy and childbirth. The risk is especially high to the fetus among the former patients with cyanosis and to the mother among the latter patients with Eisenmenger syndrome.

Table 5. Possible Maternal and Fetal Complications During Pregnancy in Women Following Fontan Procedure

- Systemic venous congestion
- Worsening of systemic ventricular function
- Worsening of atrioventricular valve regurgitation
- Supraventricular tachycardia
- Thromboembolism
- Paradoxical thromboembolism (in patients following fenestrated Fontan procedure in which a fenestration was created in the atrial septum)
- Abortion and premature delivery
- Low birth weight infants
- Infertility, amenorrhea