症が約7割であり(図2)、初診時の三大症状は、息切れ、咳、浮腫であった。

75%の患者において、産婦人科医もしくは一般内科医が初診医であった。初診時の血清BNP(脳性ナトリウム利尿ペプチド)値は96%の患者で100pg/mlを超えており、簡便な診断検査として有用であると判明した。

予後については、母体死亡例が4%、左心補助人工心臓を装着し、移植待機となった重症心不全例が2%であった。退院症例においては、平均約10カ月の観察期間の後、心機能が回復した患者が約6割、回復しなかった患者が約4割であった。

これらの臨床像についての国際比較を表2に挙げる。日本の臨床像は米国と相似しており、先進国における周産期心筋症像が一致することが初めて示された[17]。

アンケート調査結果の詳細については、国立循環器病研究センターホームページに掲載している[18]。今後の診療のご参考にしていただければ幸いである。

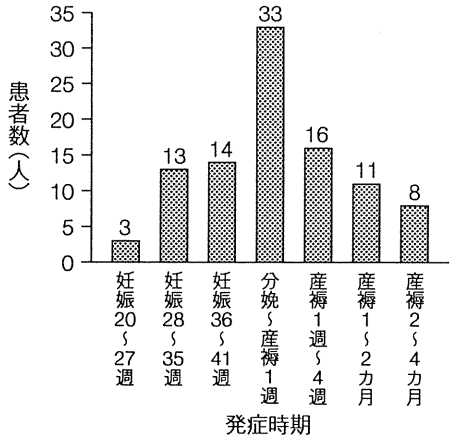


図2 日本における周産期心筋症の発症時期

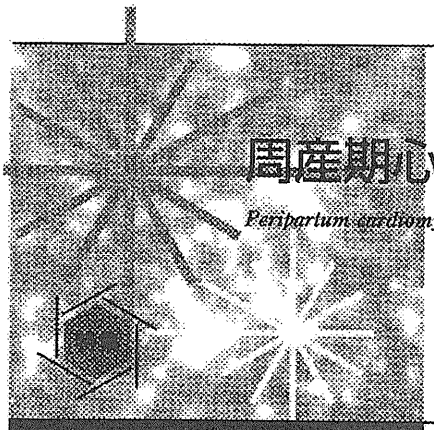
表2 周産期心筋症の臨床像についての国際比較

	日本 2009年 n=102	米国 2005年 n=100	南アフリカ 2005年 n=100	ハイチ 2005年 n=98
平均年齢(歳)	32.7	30.7	31.6	31.8
平均妊娠回数(回)	1.7	2.6	3	4.3
初産婦(%)	55	37	20	24
アフリカ系人種(%)	0	19	100	98
高血圧・妊娠高血圧症候群の合併(%)	42	43	2	4
子宮収縮抑制薬の使用(%)	14	19	9	0
多胎妊娠(%)	15	13	6	6
死亡率(%)	4	9	15	15

(文献[17]より改変引用)

□■□文 献□■□

1) Demakis JG, et al : Circulation 44 : 964, 1971. 2) Elkayam U, et al : Circulation 111 : 2050, 2005. 3) Mielniczuk LM, et al : Am J Cardiol 97 : 1765, 2006. 4) Brar SS, et al : Am J Cardiol 100 : 302, 2007. 5) Pearson GD, et al : JAMA 283 : 1183, 2000. 6) Bultmann BD, et al : Am J Obstet Gynecol 193 : 363, 2005. 7) Ansari AA, et al : Clin Immunol Immunopathol 68 : 208, 1993. 8) Geva T, et al : Am Heart J 133 : 53, 1997. 9) Hilfiker-Kleiner D, et al : Cell 128 : 589, 2007. 10) Hilfiker-Kleiner D, et al : J Am Coll Cardiol 50 : 2354, 2007. 11) Meyer GP, et al : J Med Case Reports 4 : 80, 2010. 12) Sliwa K, et al : Circulation 121 : 1465, 2010. 13) Amos AM, et al : Am Heart J 152 : 509, 2006. 14) Demakis JG, et al : Circulation 44 : 1053, 1971. 15) Sliwa K, et al : Int J Cardiol in press, 2010. 16) Elkayam U, et al : N Engl J Med 344 : 1567, 2001. 17) Sliwa K, et al : Lancet 368 : 687, 2006. 18) 国立循環器病研究センターホームページ循環器情報サービス:医療従事者向け<http://www.ncvc.go.jp/cvdinfo/pro/peripartum_cardiomyopathy.html> 一般向け<http://www.ncvc.go.jp/cvdinfo/disease/peripartum_cardiomyopathy.html>



知っておきたい二次性心筋症

周産期心筋症(産褥期心筋症)

Peripartum cardiomyopathy

神谷千津子 *KAMIYA Chizuko*　瀧原 圭子* *TAKIHARA Keiko*

心筋症・心筋炎－基礎と臨床の最前線2010　Key words: 周産期心筋症　産褥期(性)心筋症　心不全　プロラクチン

診断基準

1971年にDemakisらが提唱した,「①分娩前1ヵ月から分娩後5ヵ月以内に新たに心不全の症状が出現,②心疾患の既往がない,③他に心不全の原因となるものがない」[1]をもとに,心エコー上の左室収縮能低下や拡大所見を加えて,「④左室駆出率(LVEF)<45~55%,左室短縮率<30%,左室拡張末期径/体表面積≧2.7cm/m²」などが,診断基準として広く用いられている.

もともと,分娩前1ヵ月よりも以前に心不全を発症した症例では,その原疾患が妊娠による循環負荷やホルモン負荷により心不全症状が出てきた潜在性特発性拡張型心筋症であるということを否定し得ないため,①項が設定されていた.しかしながら,2005年にElkayamらが,妊娠・産褥期に心筋症を発症した123症例のうち23症例が,診断基準に含まれていない妊娠16~36週の発症であり,その患者背景,発症時の臨床所見,予後などは,従来の診断基準に合致する周産期心筋症症例とほぼ同等であったと報告した[2].この結果をもとに,分娩1ヵ月前以前の発症の患者も含むよう,①項を妊娠中もしくは妊娠6ヵ月以降から分娩後5ヵ月以内と変更する動きもある.

このように診断基準もまだ未確立ではあるが,周産期心筋症に特化した検査所見はなく,あくまで除外診断であることを念頭に置き,他の二次性心筋症や心筋梗塞,心筋炎など,鑑別疾患をきちんと除外して診断にあたることが重要である.

発症頻度

1990~2002年のアメリカ全土の人口ベース発症率調査においては,周産期心筋症の発症は3,189出産に1例の確率であった[3].興味深いことに,1990~1993年が4,350出産に1例の確率であったのが,2000~2002年では,2,229出産に1例と,年々発症率は増加してきている.その要因について,妊婦の高齢化と生殖医療の進歩による多胎妊娠の増加傾向に加えて,医療従事者における疾患認識が向上し診断数も増加したため,と報告者らは考察している.

従来,ハイチや南アフリカなど,中南米・アフリカの一部の国においては,周産期心筋症を高頻度に認め,黒人に多いと報告されてきた.実際に,南カリフォルニアでの周産期心筋症発症率を人種別にまとめた報告によると,黒人>アジア人>白人>ヒスパニックの順であり,それぞれ1/1,421出産,1/2,675出産,1/4,075出産,1/9,861出産

国立循環器病研究センター周産期・婦人科 *大阪大学保健センター・大阪大学大学院医学研究科循環器内科学 教授

の発症率であった[4]．このような人種による発症率の違いの原因は分かっておらず，その発症機序に遺伝的素因があるとも推測されている．

わが国においては，2009年に厚生労働省科学研究の一環として全国調査が行われ，約2万出産に1例の発症率であることが判明した．欧米の発症率に比し，かなり低値であるが，その原因として，人種や生活習慣(妊娠年齢期の女性の肥満・高血圧が少ないなど)の差異だけでなく，疾患概念が普及しておらず，未診断症例がある可能性も考慮される．

病　　因

周産期心筋症の病因についてはさまざまな説があるが，まだ原因は不明である．病態が拡張型心筋症に類似していることから，診断基準の項で述べたように，もともと特発性拡張型心筋症が潜在しており，それが妊娠・出産に伴う心負荷により顕在化したという説や，心筋炎であるという説もある．しかしながら，同年代女性における特発性拡張型心筋症や心筋炎の発症率よりもかなり高率に妊産褥婦に発症することから，アメリカNIHのワークショップ・グループにおいても，妊娠自体が発症に関与している別な病態と結論付けられている[5]．

以下，病因についてのいくつかの説を取り上げて解説する．

1. ウイルス感染説

妊娠中は免疫反応が低下しており，未感染のウイルスに感染した際に心筋炎を起こしやすい，もしくは既感染のウイルスによる炎症再燃が起こりやすい状態と考えられる．実際に，周産期心筋症患者の心筋生検標本の病理診断から心筋炎が疑われる確率は，8～78%と報告されている．報告ごとに数値が大きく異なっているのは，心不全発症から心筋生検施行までの期間の長さの違いや，病理診断でボーダーライン心筋炎と診断された症例も含めるかどうかの違いによるとされる．2005年Bultmannらは，心筋生検で得られた組織にてウイルスのゲノム解析を施行し，周産期心筋症患者の約30%に間質の炎症所見(CD3+Tリンパ球やCD68+マクロファージの間質浸潤)とPCR法にてウイルス遺伝子を認めた．一方，対照群として拡張型心筋症などそのほかの心筋症患者においても同様の検査を実施し，同じく約30%にPCR法にてウイルス遺伝子を認めたが，間質の炎症所見は認めなかった．周産期心筋症患者におけるウイルス陽性例と陰性例との間に心機能も含めた母体予後の差はなかったと報告した[6]．

2. 異常免疫反応説

これまでに，胎児由来の造血細胞のキメラが妊娠中の母体血液中に出現することが知られている．このような胎児由来の細胞が心筋内に生着し，免疫反応が低下している妊娠中には炎症を起こさなかったものが，出産後免疫反応が回復するとともに抗原と認識され，局所的な炎症を引き起こす可能性が考えられている[7]．また，血清中の心筋蛋白に対する自己抗体量が特発性心筋症患者よりも周産期心筋症患者において高値であり，自己免疫異常が発症に関与しているという説や，周産期心筋症患者の血中TNF-αやCRPが有意に増加し，その値が初診時心機能と相関しているため，異常な炎症メカニズムが発症に関与しているのでは，との説もある．

3. 妊娠に伴う循環負荷への反応説

一般に，妊娠中には循環血液量や心拍出量は増大し血管抵抗は減少する．このような循環生理の変化に伴い，正常心においても妊娠後期から産褥にかけて一過性に心収縮力が低下することが報告されている[8]．このような変化が過剰に発現した結果，周産期心筋症を発症するという仮説もあるが，これを証拠付ける報告はまだない．

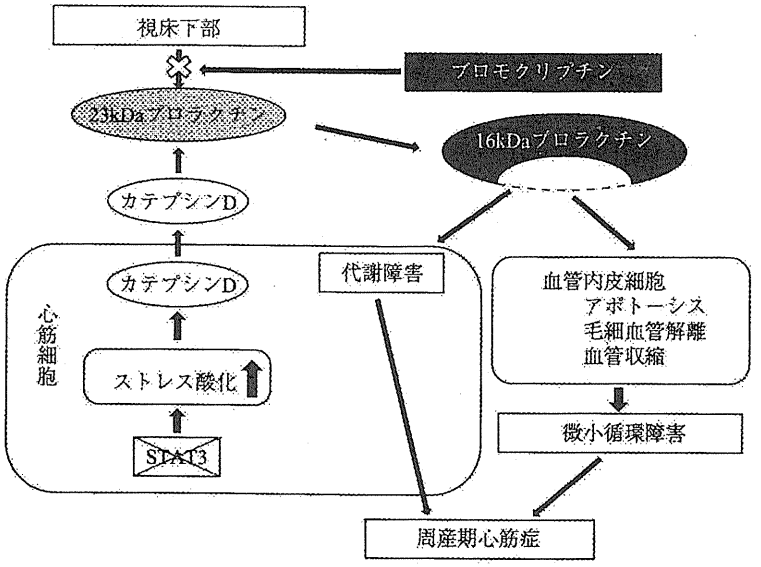


図1 異型プロラクチンによる周産期心筋症発症のメカニズム
STAT3(転写因子:酸化ストレスを抑制し血管新生に関与)が減少することにより,心筋細胞内で酸化ストレスが増加し,カテプシンDという酵素の産生が増強される.このカテプシンDにより,16kDaの異型プロラクチンが血中で増加し,内皮細胞のアポトーシスや血管収縮,心筋細胞の代謝異常を引き起こし,心筋症が発症すると考えられる.(文献9より引用改変)

4. 内分泌異常説

2007年にHilfiker-Kleinerらは,心筋特異的にSTAT3蛋白をノックアウトした雌マウスにおいて,妊娠出産を契機として高率に心筋症・心不全を発症することに注目し,周産期心筋症の発症メカニズムについての研究結果を報告した[9].心筋でのカテプシンDという蛋白分解酵素の発現亢進により,血中で23kDaのプロラクチンが切断され16kDaのプロラクチンが増加していることが明らかにされた.この16kDaのプロラクチンは血管新生に対して抑制的に作用することが知られており,この異型プロラクチンが内皮細胞や心筋細胞を傷害することにより心筋症を発症すると考えられた(図1).また,このマウスに抗プロラクチン薬であるブロモクリプチンを投与したうえで妊娠分娩させると心筋症を発症しないこと,実際の周産期心筋症患者の血清中にも異型プロラクチンが存在しており,周産期心筋症既往患者の次回妊娠時にブロモクリプチンを投与すると,心筋症の発症を予防できることもあわせて報告した[9].

その後,ブロモクリプチン(抗プロラクチン)療法(後述)が有効であるとの報告がいくつかなされている[10]~[12].

危険因子

前述のように,疾病原因はいまだ特定されていないが,数々の危険因子については報告されてきている.まず,診断基準を提唱したDemakisらは,多産,高齢,多胎,妊娠高血圧症候群,黒人を危険因子としてあげている.ほかに,子宮収縮抑制剤の使用や慢性高血圧合併,喫煙,肥満なども患者群で有意に多いことが指摘されている[13].

わが国においては,2009年の全国調査で,高齢,慢性高血圧や妊娠高血圧症候群の合併,子宮収縮抑制剤の使用や多胎が危険因子であることが判明した.これらの危険因子も含めたわが国における周産期心筋症の臨床像は,アメリカと相似していることが判明した(表1).しかしながら,少子化の影響か,わが国における周産期心筋症患者の半数以上が初産婦であった.また,35歳以上に限った発症率は1万出産に1例であり,高齢でかつ高

表1 周産期心筋症の臨床像についての国際比較

	日本 2009年 n=102	アメリカ 2005年 n=100	南アフリカ 2005年 n=100	ハイチ 2005年 n=98
平均年齢(歳)	32.7	30.7	31.6	31.8
平均妊娠回数(回)	1.7	2.6	3	4.3
初産婦(%)	55	37	20	24
アフリカ系人種(%)	0	19	100	98
高血圧・妊娠高血圧症候群の合併(%)	42	43	2	4
子宮収縮抑制剤の使用(%)	14	19	9	0
多胎妊娠(%)	15	13	6	6
死亡率(%)	4	9	15	15

(Sliwa K, et al：Lancet 368：687-693, 2006より引用改変)

血圧などの危険因子を併せ持つ症例においては，注意が必要と考えられた．

予　後

当初Demakisらは，半数は心機能が正常に回復し，半数は心機能低下が残存すると報告した[14]．後者の一部が重症化し，死亡もしくは心移植を受けることとなる．その後，さまざまな国や施設で検討されたが，左室機能が改善する率が7～50%，死亡率が4～80%と，報告ごとに大きく異なっており，人種や医療水準の違いが影響していると考えられる．最近の欧米からの報告では，死亡率が3～6%であり，依然，重症例は致死的であると考えられ慎重に治療にあたる必要がある．

また，2006年のAmosらの報告によると，発症後平均約4年間の追跡期間で，約6割が心機能改善し，残りの4割が心機能低下，最重症の1割が心機能増悪して心移植が必要であった．心移植により，死亡例は1例も認めなかった．左心補助装置や心移植により死亡例がなかったこと，適切な内科治療(対象患者の9割がACE阻害薬，6割がβ遮断薬を内服)により，心機能改善例がこれまでの報告よりも多かったことをあげて，周産期心筋症の予後が改善してきていると結論付けている[13]．

これまでに，予後予測因子として，初診時もしくは発症2ヵ月後のLVEF，左室拡張末期径(LVDd)，左室内血栓の有無，人種などがあげられている．

治療法

周産期心筋症の治療については，一般的な心不全に対する治療が広く行われている．重症例では，急性期にカテコラミン治療に加え，IABP(大動脈内バルーンパンピング)やPCPS(経皮的心肺補助装置)を使用する．慢性期には，ACE阻害薬やβ遮断薬，利尿剤などの内服治療が行われるが，治療抵抗性の症例では，心臓移植や死に至ることもある．

また心不全に対する対症療法以外にも，自己免疫性心筋炎を疑う症例でのステロイド・免疫抑制剤の使用や，大量γグロブリン療法などが試みられてきた．前述の抗プロラクチン療法においては，2010年にSliwaらが南アフリカにおける周産期心筋症患者20人を，標準治療にブロモクリプチンを投与した群(PPCM-Br群：10人)と標準治療のみの群(PPCM-Std群：10人)の2群に分け，半年間予後を追跡したところ，患者背景に有意差がなかったにもかかわらず，死亡率はPPCM-Br群10%に対しPPCM-Std群で40%，生存者の半年後のLVEFはPPCM-Br群58%に対しPPCM-Std群で36%と，予後に大きな差を認めた[12]．しかし，対照であるPPCM-Std群の予後が一般に比べて悪すぎるとの指摘もあり，今後のさらなる検討が

表2 周産期心筋症患者の次回妊娠・出産時における母体合併症の発生率

	心不全症状の出現	周産期における20%以上のLVEF低下	再妊娠前と比較し，最終経過観察時のLVEF低下	死亡
Group 1(23人)	6人(26%)	4人(17%)	2人(9%)	0人
Group 2(12人)	6人(50%)	4人(33%)	5人(42%)	3人(25%)

LVEF：左室駆出率
Group 1：心筋症発症後の心機能改善群：LVEF≧50%
Group 2：心筋症発症後の心機能低下群：LVEF <50%
(文献16より引用改変)

待たれるところである．

慢性期，心機能回復例における内服治療の中止については，明確な基準はない．ACE阻害薬とβ遮断薬を併用し，心機能が回復した周産期心筋症患者において，どちらか一方を中止した6人と両剤を中止した5人の全員が，平均2.5年の経過観察中，心機能は保たれたままであったとの報告[14]がある一方，心機能回復例でも心室細動などが原因で突然死することがあり，長期に経過観察が必要との報告[15]もある．

再妊娠による再発率

妊娠・分娩が本疾患の発症・進行に関与していると考えられるため，周産期心筋症既往者の再妊娠については，高いリスクが伴う．

次子を分娩した周産期心筋症既往患者35人を，心筋症発症後の心機能改善群(Group 1：LVEF≧50%)23人と心機能低下群(Group 2：LVEF<50%)12人に分けて解析した結果，心不全発症例がGroup 1で6人(26%)，Group 2で6人(50%)であった．Group 1で死亡例はなかった一方，Group 2では3人(25%)が死亡した(2人が突然死，1人が心不全死)(表2)．一方，児の予後については，Group 1で3人(13%)，Group 2で6人(50%)が早産に至ったが，新生児死亡例はなかった[16]．

この結果を踏まえ，発病後，慢性期にも心機能低下が持続している症例においては，再妊娠は回避すべきであると考えられる．しかしながら，心機能回復症例においてどう対応するかは，まだ一定した見解のないところである．

おわりに

息切れや体重増加，浮腫などの心不全症状は，多くの正常妊婦も訴える症状であり，その軽重を見極めることは難しい．しかしながら，診断時の心機能が予後に影響することが分かっており，早期診断，早期治療が及ぼす効果は大きい．心不全症状を訴える妊産褥婦の診察においては，周産期心筋症も鑑別疾患にあげ，診療にあたることが非常に重要である．

文　献
1) Demakis JG, Rahimtoola SH：Peripartum cardiomyopathy. Circulation 44：964-968, 1971.
2) Elkayam U, Akhter MW, Singh H, et al：Pregnancy-associated cardiomyopathy：clinical characteristics and a comparison between early and late presentation. Circulation 111：2050-2055, 2005.
3) Mielniczuk LM, Williams K, Davis DR, et al：Frequency of peripartum cardiomyopathy. Am J Cardiol 97：1765-1768, 2006.
4) Brar SS, Khan SS, Sandhu GK, et al：Incidence, mortality, and racial differences in peripartum cardiomyopathy. Am J Cardiol 100：302-304, 2007.
5) Pearson GD, Veille JC, Rahimtoola S, et al：Peripartum cardiomyopathy：National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA 283：1183-1188, 2000.

6) Bultmann BD, Klingel K, Nabauer M, et al : High prevalence of viral genomes and inflammation in peripartum cardiomyopathy. Am J Obstet Gynecol 193 : 363-365, 2005.
7) Ansari AA, Neckelmann N, Wang YC, et al : Immunologic dialogue between cardiac myocytes, endothelial cells, and mononuclear cells. Clin Immunol Immunopathol 68 : 208-214, 1993.
8) Geva T, Mauer MB, Striker L, et al : Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. Am Heart J 133 : 53-59, 1997.
9) Hilfiker-Kleiner D, Kaminski K, Podewski E, et al : A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 128 : 589-600, 2007.
10) Hilfiker-Kleiner D, Meyer GP, Schieffer E, et al : Recovery from postpartum cardiomyopathy in 2 patients by blocking prolactin release with bromocriptine. J Am Coll Cardiol 50 : 2354-2355, 2007.
11) Meyer GP, Labidi S, Podewski E, et al : Bromocriptine treatment associated with recovery from peripartum cardiomyopathy in siblings : two case reports. J Med Case Reports 4 : 80, 2010.
12) Sliwa K, Blauwet L, Tibazarwa K, et al : Evaluation of bromcriptine in treatment of acute severe peripartum cardiomyopathy. A proof-of-concept pilot study. Circulation 121 : 1465-1473, 2010.
13) Amos AM, Jaber WA, Russell SD : Improved outcomes in peripartum cardiomyopathy with contemporary. Am Heart J 152 : 509-513, 2006.
14) Demakis JG, Rahimtoola SH, Sutton GC, et al : Natural course of peripartum cardiomyopathy. Circulation 44 : 1053-1061, 1971.
15) Sliwa K, Forster O, Tibazarwa K, et al : Long-term outcome of peripartum cardiomyopathy in a population with high seropositively for human immunodeficiency virus. Int J Cardiol (in press).
16) Elkayam U, Tummala PP, Rao K, et al : Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 344 : 1567-1571, 2001.

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

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%

Released online December 17, 2011
Mailing address: Scientific Committee of the Japanese Circulation Society, 8th Floor CUBE OIKE Bldg., 599 Bano-cho, Karasuma Aneyakoji, Nakagyo-ku, Kyoto 604-8172, Japan. E-mail: meeting@j-circ.or.jp
This English language document is a revised digest version of Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heart Disease reported at the Japanese Circulation Society Joint Working Groups performed in 2009. (website: http://www.j-circ.or.jp/guideline/pdf/JCS2010niwa.d.pdf)
Joint Working Groups: The Japanese Circulation Society, Japan Society of Obestetrics and Gynecology, Japanese Society of Pediatric Cardiology and Cardiac Surgery, The Japanese Society of Cardiovascular Surgery, Japanese College of Cardiology
ISSN-1346-9843 doi:10.1253/circj.CJ-88-0023

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.[35]

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

Table 6. Characteristics of Drugs for the Treatment of Pulmonary Hypertension During Pregnancy and Lactation

Drug	Class	Pregnancy categories	Characteristics/ adverse effects	Teratogenicity	Breast feeding	Package insert*1	
						Pregnancy	Lactation
Beraprost	Prostacyclin	B	Oral	Absent	Probably compatible	1	1
Epoprostenol	Prostacyclin	B	Drip infusion	Absent	Probably compatible	2	1
Bosentan	Endothelin receptor antagonist	X	Oral, Hepatic disorder	Unknown*2	Potential toxicity	1	2
Sildenafil	PDE III inhibitor		Oral, Visual disorder			2	1

PDE III, phosphodiesterase III.
Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)"[46] (Blank columns represent no information in the source material).
*1Information on the use during pregnancy and lactation in the package insert.
1. Contraindication: This drug should not be administered to women who are or may be pregnant. Treatment should be discontinued without delay when pregnancy is detected. The drug should not be given to lactating women, and, when treatment is necessary, should be given after lactation is stopped.
2. Relative contraindication: The drug should be used when the benefits of use outweigh the risks. It is desirable that the treatment be avoided in women who are or may be pregnant. The safety in pregnant women has not been established.
*2Bosentan has been reported teratogenic in animals, but the risk for teratogenicity is unclear in humans.
[Precautions]
1) Indications and contraindications should be confirmed when considering the use during pregnancy.
2) When drugs contraindicated or not indicated for pregnant women in the package inserts, the physicians must fully explain the use of such drugs to the patients and their families and obtain informed consent.

Table 7. Classification of Valvular Heart Diseases by Maternal and Fetal Risks

	Low maternal/fetal risk factors	High maternal/fetal risk factors
Aortic stenosis	Asymptomatic; Normal left ventricular function; Mean pressure gradient <25 mmHg; Orifice area >1.5 cm^2	Severe stenosis; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Aortic regurgitation	NYHA Class I to II; Normal left ventricular function	NYHA Class III to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral stenosis	No severe pulmonary hypertension; Orifice area >1.5 cm^2; Mean pressure gradient <5 mmHg	NYHA Class II to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral regurgitation	NYHA Class I to II; Normal left ventricular function	NYHA Class III to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral valve prolapse	No mitral regurgitation, or Mild to moderate mitral regurgitation but normal left ventricular function	
Pulmonary stenosis	Mild to moderate stenosis	

• High maternal/fetal risk factors
- Complicated with severe pulmonary hypertension (pulmonary artery pressure is ≥75% of systemic blood pressure)
- Left ventricular dysfunction (LVEF<40%)
- Using mechanical valves requiring anticoagulation therapy
- Marfan syndrome
• Low maternal/fetal risk factors
- Normal left ventricular function (LVEF>50%)

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

2. Pulmonary Hypertension (Table 6)

In women with pulmonary hypertension, pregnancy will increase pulmonary artery pressure, worsen right heart failure, and worsen ventilation-perfusion ratio mismatch. The risk during pregnancy and childbirth in patients with pulmonary hypertension is extremely high. It is strongly recommended that women with pulmonary hypertension avoid pregnancy by using reliable contraception, and prompt artificial termination of pregnancy, if occurs, should be considered whenever necessary.[70–72] If a patient decided to continue pregnancy after understanding the risk, she must be hospitalized at an appropriate timing to monitor the progress and perform childbirth under careful management by a special team.[73–75] Since death immediately after childbirth may often occur, the mother must be monitored for about 1 week in the intensive care unit. The outcome does not differ by delivery method (cesarean section vs. vaginal delivery) and anesthesia (general anesthesia vs. local anesthesia).[76]

3. Valvular Heart Diseases

Table 7 describes the guidelines for pregnancy and childbirth in patients with valvular heart diseases[48] and Table 8 lists anticoagulation and antiplatelet therapies during pregnancy.

Figure shows a flow chart of anticoagulation therapy during pregnancy in patients using mechanical valves that is commonly practiced in Japan empirically rather than based on scientific data.[77] During the first trimester of pregnancy, patients should receive unfractionated heparin or low molecular weight heparin[78,79] rather than warfarin[80,81] which may cause malformation in the fetus. At 14 weeks of gestation or thereafter, either subcutaneous heparin or oral warfarin should be selected. Since heparin is not highly reliable in terms of the prevention of thrombosis, oral warfarin therapy is a preferable method for the mother. At 36 weeks of gestation, oral warfarin should be replaced by continuous intravenous administration of heparin. Cesarean section is preferable since staff members and instrument can be scheduled in advance.

Table 8. Characteristics of Anticoagulation/Antiplatelet Drugs Used During Pregnancy and Lactation

Drug	Class	Pregnancy categories	Characteristics/ adverse effects	Teratogenicity	Breast feeding	Package insert*	
						Pregnancy	Lactation
Warfarin	Coumarin delivative	D	- Teratogenic (osteogenesis/ chondrogenesis, cerebral nervous system) - Bleeding complication in the fetus	Present	Compatible	1	1
Heparin	Unfractionated heparin	C	- Promote decal cification during long-term treatment (bone fracture in the mother) - Higher incidence of thrombosis than warfarin	Absent	Compatible	1	
Enoxaparin	Low molecular weight heparin	B	- Heparin-induced thrombocytopenia has been reported - Not indicated for the prevention of thrombosis in patients with cardiovascular disease	Absent	Compatible	2	2
Dalteparin		B		Absent	Compatible	1	1
Aspirin (low-dose)	Antiplatelet effect	C	- Considered relatively safe - Contraindicated in 28 weeks of gestation or thereafter regardless of the dose	Absent	Potential toxicity	2	1
Dipyridamole	Antiplatelet effect	B	Hypotension, worsening of anginal symptoms	Absent	Probably compatible	2	1
Ticlopidine	Antiplatelet effect	B	Bleeding, liver disorder	Absent	Potential toxicity	2	1

Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)".[40]
*Information on the use during pregnancy and lactation in the package insert (Blank columns represent no information in the source material).
1 Contraindication: This drug should not be administered to women who are or may be pregnant. Treatment should be discontinued without delay when pregnancy is confirmed. The drug should not be given to lactating women, and, when treatment is necessary, should be given after lactation is stopped.
2 Relative contraindication: The drug should be used when the benefits of use outweigh the risks. It is desirable that the treatment be avoided in women who are or may be pregnant. The safety in pregnant women has not been established. It is desirable that the drug be given after lactation is stopped.
[Precautions]
1) Indications and contraindications should be confirmed when considering the use during pregnancy.
2) When drugs contraindicated or not indicated for pregnant women in the package inserts, the physicians must fully explain the use of such drugs to the patients and their families and obtain informed consent.

4. Aortic Diseases

See Table 9 for recommendations for patients with Marfan syndrome.[82,83]

See Table 10 for recommendations for patients with Takayasu disease.[84,85]

Patients with unrepaired congenital coarctation of the aorta may experience severe complications such as hypertension, left heart failure, aortic aneurysm formation and aortic dissection during pregnancy. When the patient shows aortic dilatation and develop hypertension during pregnancy, management with bed rest and β-blockers are required. Periodic blood pressure monitoring is necessary since a decrease in blood pressure reduces blood flow in the placenta. It is preferable that the patient undergo surgery or catheter interv tion to repair coarctation of the aorta before pr e risk during pregnancy to the mother and fetus is . patients following repair of coarctation of the aorta. However, patients with hypertension or aortic dilatation should be managed with β-blockers.

5. Cardiomyopathy

Women with hypertrophic cardiomyopathy, even those with chest pain, exertional dyspnea and/or syncope before pregnancy, will rarely experience worsening of signs/symptoms during pregnancy, and may tolerate pregnancy in most cases. The risk is believed high in those with a maximum wall thickness of $\geq$ 30 mm, those with a history of cardiac arrest or sustained ventricular tachycardia, those with recurrent syncope, and those with a family history of sudden death: The risk of pregnancy/childbirth should be carefully evaluated for these patients.[86,87]

Fatal heart failure is rare in women with dilated cardiomyopathy when heart failure is compensated and remained in NYHA Class I, and drug therapy may be discontinued during pregnancy. However, severe heart failure may develop in some cases during the third trimester, and careful consideration is required even for patients with mild heart failure.[88,89]

Peripartum cardiomyopathy develops most commonly in the first month after childbirth. Cardiac function returns to normal by 6 months after childbirth in about 50% of patients, but the prognosis of patients with persistent and progressive

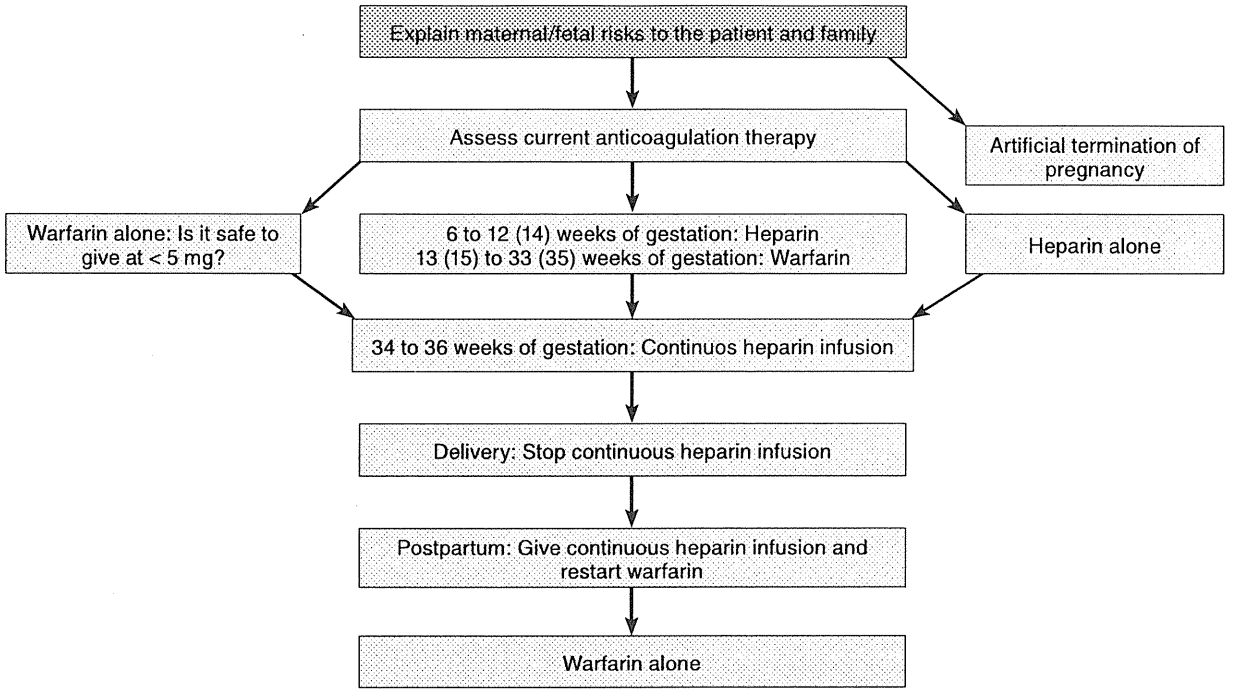


Figure. Flow chart of anticoagulation therapy in pregnant women with mechanical valves who have received Warfarin before pregnancy.

Table 9. Important Points of Management for Patients With Marfan Syndrome During Pregnancy and Childbirth

1. Explain that there is a 50% possibility of inheriting the disease.
2. Encourage the patient to undergo surgery before pregnancy, if indicated.
3. Instruct the patient to avoid pregnancy when the ascending aortic diameter (including Valsalva sinus) is 44 mm or larger or when aortic dissection is present. Patients with aortic diameter of 43 mm or smaller should be explained that they can become pregnant but may develop aortic dissection.
4. Patients with an ascending aortic diameter of <40 mm may have normal vaginal delivery.
5. Mitral regurgitation should be treated according to the guidelines for the treatment of valvular heart diseases.
6. β-blockers should be given whenever necessary with careful consideration of the potential effects on the mother and fetus.
7. Perform strict blood pressure control and pain management.

Table 10. Important Points of Management for Patients With Takayasu Disease During Pregnancy and Childbirth

1. It is reported that patients with untreated atypical coarctation of abdominal aorta may develop renal hypertension, which may lead to heart failure and renal failure. The prognosis of these patients is poor since sepsis and pregnancy-induced hypertensive nephropathy may develop.
2. Atypical coarctation of the aorta should be treated according to the recommendations for the treatment of coarctation of the aorta.
3. Aortic regurgitation should be treated according to the recommendations for the treatment of valvular heart diseases.
4. Aortic aneurysms (including annuloaortic ectasia) should be treated according to the recommendation for Marfan syndrome.
5. Ischemic heart disease (coronary ostial narrowing): Consider for surgery before pregnancy.
6. Hypertension should be treated with β-blockers. ACE inhibitors and angiotensin receptor blockers should be avoided.
7. Steroid therapy should be continued, but treatment at higher doses is rarely required.
8. Patients should be observed for autoimmune disorders and connective tissue diseases (collagen diseases).

ACE, angiotensin converting enzyme.

Table 11. Definition and Classification of Pregnancy Induced Hypertension: Proposed by Japan Society of Obstetrics and Gynecology, 2005

1. Term

Pregnancy toxemia should be referred to as pregnancy induced hypertension (PIH).

2. Definition

PIH is defined as hypertension with or without proteinuria developing during the period from 20 weeks of gestation to 12 weeks of postpartum. Hypertension due to other complications is not PIH.

3-1. Classification of PIH

(1) Preeclampsia
Preeclampsia is defined as hypertension with proteinuria that develops at 20 weeks of gestation or thereafter and subsided by 12 weeks of postpartum.

(2) Gestational hypertension
Gestational hypertension is defined as hypertension that developed 20 weeks of gestation or thereafter and subsided by 12 weeks of postpartum.

(3) Superimposed preeclampsia
Patients with superimposed preeclampsia include:
1) Women who have hypertension before pregnancy or by 20 weeks of gestation and develop proteinuria at 20 weeks of gestation or thereafter.
2) Women who have hypertension and proteinuria before pregnancy or by 20 weeks of gestation and experience worsening of hypertension and/or proteinuria at 20 weeks of gestation or thereafter.
3) Women who have proteinuria as the only sign of renal disease before pregnancy or by 20 weeks of gestation and develop hypertension at 20 weeks of gestation or thereafter.

(4) Eclampsia
Eclampsia is defined as the first onset of convulsions not related to epilepsy or secondary convulsions at 20 weeks of gestation or thereafter. Eclampsia is classified into antepartum eclampsia, intrapartum eclampsia and puerperal eclampsia according to the timing of onset.

3-2. Subclassification based on clinical findings

(1) Disease type by clinical findings

	Hypertension	Proteinuria
Mild	When one of the two criteria is met: 1. 140mmHg≤ systolic blood pressure <160mmHg 2. 90mmHg≤ diastolic blood pressure <110mmHg	Urinary protein excretion is at least 300mg/day and less than 2g/day in a 24-hour urine specimen
Severe	When one of the two criteria is met: 1. Systolic blood pressure is ≥160mmHg 2. Diastolic blood pressure is ≥110mmHg	Urinary protein excretion is ≥2g/day, or spot urinary protein level is ≥300mg/dl in more than 3 consecutive samples from fresh urine

(2) Disease type by timing of onset
Those developing by 32 weeks of gestation are referred to as early onset type, and those developing at 32 weeks of gestation or thereafter as late onset type.

[Remarks]

(1) Gestational proteinuria (proteinuria that is first detected at 20 weeks of gestation or thereafter and subsides by 12 weeks of postpartum) is not included in PIH typing.

(2) Chronic hypertension may often lead to superimposed preeclampsia, and should be managed carefully as in the case of PIH. Worsening of chronic hypertension is not included in PIH typing.

(3) Pulmonary edema, cerebral hemorrhage, premature separation of the normally implanted placenta, and HELLP syndrome* are not always caused by PIH, but are critical illness closely related to PIH. These findings are not included in PIH typing.

(4) The type of PIH is expressed using h and H for mild and severe hypertension, p and P for mild and severe proteinuria, EO for early onset type, LO for late onset type, S for superimposed type, and C for eclampsia.
For example, the type of preeclampsia may be expressed with Hp-EO and hP-LO, gestational hypertension with H-EO and h-LO, superimposed preeclampsia with Hp-EOS and hP-LOS, and eclampsia with HP-EOSC and hP-LOSC.

*HELLP syndrome is characterized by Hemolysis, Elevated Liver enzyme and Low Platelets, and develops during pregnancy (often at 27 weeks of gestation or thereafter) and the puerperal period.
Cited from *Acta Obstetrica et Gynaecologica Japonica* 2006; **58:** N61–N70.[103]

left ventricular dysfunction is poor.[88,89] In patients who continue to show a left ventricular ejection fraction (LVEF) of ≤ 50% after childbirth, cardiac function may often decrease to cause death during or after the next pregnancy. Contraception is strongly recommended for such patients.[90] Most effects on the fetus develop in the third trimester or after birth, and the incidences of low birth weight infants and stillbirth are slightly higher than in healthy women.

6. Arrhythmias

Patients with congenital heart disease associated with arrhythmia are often treated and monitored carefully for arrhythmia during pregnancy. In patients following repair of congenital heart disease, arrhythmia may newly develop or worsen during pregnancy and childbirth.[91,92] Since atrial flutter/fibrillation, atrial tachycardia, ventricular tachycardia, severe atrioventricular block, and other conditions may cause significant hemodynamic changes that highly affect the mother and fetus, appropriate diagnosis and emergency treatment are commonly required.[73,93] Pregnant women with risk factors for development of arrhythmia (eg, those with heart failure, those with pre-existing arrhythmia before pregnancy, and those with a history of tachyarrhythmia) should undergo regular checkups more frequently during pregnancy.

Table 12. Characteristics of Antihypertensive Drugs Commonly Used During Pregnancy and Lactation

Drug	Class	Pregnancy categories*1	Characteristics/ adverse effects	Teratogenicity*1	Breast feeding	Package insert*2	
						Pregnancy	Lactation
Methyldopa	Central antihypertensive	B	Lassitude, thirst Used in Europe and the United States	Absent	Probably compatible	2	1
Clonidine	Central antihypertensive	C	Few reports	Absent	Probably compatible	2	
Atenolol	β-blocker	D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Propranolol	β-blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Metoprolol	β-blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	1	1
Oxprenolol	β-blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	1	1
Labetalol	β-blocker	C	IUGR, hypoglycemia, bradycardia	Absent	Probably compatible	1	1
Sotalol	β-blocker	B→D	Bradycardia	Absent	Potential toxicity	2	1
Hydralazine	Peripheral vasodilator	C	Headache, neonatal thrombocytopenia	Absent	Probably compatible	2	1
Nifedipine Nicardipine	Calcium channel blocker	C	Headache, palpitation, hypotension	Absent	Probably compatible	1	1
Isosorbide dinitrate	Nitrate	C	Few reports	Absent	Probably compatible	2	1
Captopril*3	ACE inhibitor*3	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*3	Compatible	1	1
Enalapril*3	ACE inhibitor*3	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*3	Probably compatible	1	1
Candesartan*4 Losartan*4	Angiotensin receptor blocker*4	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*4	Probably compatible	1	1
Furosemide	Diuretic	C (D)	Disturbance of uteroplacental circulation, fetal dehydration	Absent	Probably compatible	2	1
Spironolactone	Diuretic	C (D)	Possible feminization	Absent	Probably compatible	2	1
Hydrochlorothiazide	Diuretic	C (D)	Thrombocytopenia, hemolytic anemia	Absent	Compatible	2	1

ACE, angiotensin converting enzyme; IUGR, intrauterine growth retardation.
Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)".[40]
*1B→D/C→D: Pregnancy category B or C during the first trimester but pregnancy category D during the second and third trimesters. C (D): Pregnancy category C for patients without gestational hypertension, and pregnancy category D for patients with gestational hypertension. Teratogenicity: Since ACE inhibitors have been reported to be teratogenic, strict caution should be needed for the use of these drugs even in the first trimester.
*2Information on the use during pregnancy and lactation in the package insert (Blank columns represent no information in the source material).
1. Contraindication: This drug should not be administered to women who are or may be pregnant. Treatment should be discontinued without delay when pregnancy is detected. The drug should not be given to lactating women, and, when treatment is necessary, should be given after lactation is stopped.
2. Relative contraindication: The drug should be used when the benefits of use outweigh the risks. It is desirable that the treatment be avoided in women who are or may be pregnant. The safety in pregnant women has not been established.
*3Since ACE inhibitors have been reported to be teratogenic, strict caution should be needed for the use of these drugs even in the first trimester.
*4Strict caution in terms of teratogenicity should be needed for the use of angiotensin receptor blockers, which exert their effects in a way similar to ACE inhibitors.
[Precautions]
1) Indications and contraindications should be confirmed when considering the use during pregnancy.
2) When drugs contraindicated or not indicated for pregnant women in the package inserts, the physicians must fully explain the use of such drugs to the patients and their families and obtain informed consent.

7. Ischemic Heart Disease

Although the incidence of acute myocardial infarction (AMI) during the perinatal period is quite rare (1 in 10,000 cases), the incidence is expected to increase in the future.[94,95] Smoking and hypertension are the most significant risk factors for development of AMI during the perinatal period.[96] AMI is more common in women who have had children, and the most common lesion is the anterior wall. β-blockers are the first-line therapy to prevent myocardial infarction (MI). Low-dose aspirin is effective in preventing myocardial ischemic attacks during pregnancy. Many reports have described that thrombolytic therapy for the treatment of AMI is not teratogenic to the fetus and the prognosis of the mother and fetus is favorable.[97] Percutaneous coronary intervention and coronary artery bypass

grafting during pregnancy are also effective.[98,99]

Patients with coronary aneurysms in Kawasaki disease do not have significant problems during pregnancy and childbirth when coronary stenosis is absent and cardiac function is normal. Patients who have coronary stenosis, those after MI and those after coronary intervention may experience a progression of ischemic disease or a worsening of heart failure during pregnancy and childbirth.[100,101]

8. Heart Failure

Volume overload and tachycardia during pregnancy may worsen heart failure. The severer the heart failure during pregnancy, the higher the mortality of the mother and the incidences of premature birth, intrauterine growth retardation and abortion or stillbirth. Women with NYHA Class III or severer heart failure should be recommended to avoid pregnancy and terminate pregnancy promptly when they become pregnant.[94,102] There are no established data indicating the safety of pregnancy in patients in certain levels of ejection fraction.

9. Hypertension (Tables 11,[103] 12)

Patients with hypertension may prone to have premature birth, intrauterine growth retardation, perinatal death, and other perinatal disorders related to pregnancy-induced hypertension. The incidences of premature separation of the normally implanted placenta and perinatal death are high in patients with pregnancy-induced hypertension.[104,105] They are often prone to have such as malignant hypertension, cerebral hemorrhage, heart failure, and renal dysfunction.

IV Important Points in Obstetric Management

Table 13. Expected Annual Pregnancy Rates With Different Contraceptive Methods

Methods	General use	Optimal use
No contraception	85%	85%
Coitus interruptus (extravaginal ejaculation)	27%	4%
Tracking menstrual cycle, sexual abstinence	25%	1 to 9%
Condom	15%	2%
Pessary	16%	6%
Oral contraceptives	8%	0.3%
Intrauterine contraceptive device	0.1 to 0.8%	0.1 to 0.6%
Tubal ligation	0.5%	0.5%
Vasoligation	0.15%	0.1%

Cited with modification from "Guidelines for the use of low-dose contraceptive pills: second edition" in 2006[106] proposed by Japan Society of Obstetrics and Gynecology.

Table 14. Incidence of Neurological Sequelae in Liveborn Infants by Gestational Age at Birth

	Hospitalized	Dead (%)	Disability
≤24 weeks	20	12 (60)	1 (13)
24 to 27 weeks	158	19 (12)	30 (22)
28 to 31 weeks	311	18 (6)	37 (13)
≥32 weeks	3,478	87 (3)	30 (1)

Data in 1984 to 1997 from the Maternal and Perinatal Center, Tokyo Women's Medical University Hospital.

1. Contraception (Table 13)[105]

2. Effects of Hemodynamic Condition of the Mother on the Fetus

When progressive worsening of maternal health to a life-threatening condition is expected, physicians should consider for termination of pregnancy (artificial abortion or early delivery). When the growth in the fetal head circumference stops due to progressive worsening of maternal condition, pregnancy should be terminated (for early delivery).

3. Timing of Delivery

The timing of delivery should be determined by considering the survival and incidence of neurological sequelae by weeks of gestation at delivery. The prognoses of infants born with a body weight of <1,000 g and infants born earlier than 28 weeks of gestation are poor[107] (Table 14).

4. Controlling Uterine Contraction

Patients with impending abortion or premature labor are indicated for tocolytics (Tables 15, 16),[108] while patients who need

Table 15. Methods of Administration of and Contraindications to Tocolytics

Methods of administration	
Ritodrine (β-stimulant)	Start at 50 μg/min, and increase the dose by 50 μg/min in every 10 to 20 minutes.
Terbutaline (not indicated in Japan)	Start at 10 μg/min, and increase the dose by 5 μg/min in every 10 minutes.
Magnesium sulfate	Administer 4 g intravenously over 30 minutes, and continue infusion at 2 to 4 g/hr by monitoring blood magnesium concentration in the mother until uterine contraction subsides.
Indomethacin (not indicated in Japan)	Administer 25 to 50 mg intrarectally or orally every 6 hours for ≤48 hours.
Contraindications	
Ritodrine (β-stimulant)	Poorly controlled diabetes, pulmonary hypertension
Magnesium sulfate	Hypocalcemia, myasthenia gravis, renal failure
Indomethacin (not indicated in Japan)	Peptic ulcer, blood disorders, hepatic/renal insufficiency, asthma, pancreatitis, proctitis, obstetric bleeding