表2 本稿における肺高血圧患者の重症度分類

| | 平均肺動脈圧<br>右心カテーテル検査 | 右心カテーテルが施行されなかった場合<br>ΔPG(三尖弁逆流の収縮期速度)<br>心エコー検査 |
|---|---|---|
| 重　症 | ≥40 mmHg | ≥50 mmHg |
| 軽　症 | 25～40 mmHg | 30～50 mmHg |
| 正　常 | ≤25 mmHg | ≤30 mmHg |

(文献34より)

た[31]。心機能検査は妊娠中，分娩後に行われた。肺高血圧症の妊娠リスクを説明し，妊娠継続の意思のある患者は妊娠を継続したが，妊娠初期に人工妊娠中絶を選択，または自然流産となった患者もいた。自然陣痛発来した患者は基本的に経腟分娩を施行した。子宮頸部成熟が未熟であるが早期娩出が必要な場合は，帝王切開を施行した。妊娠前，妊娠中，分娩後のNYHA class分類[33]を評価した。

### 1 検討項目

家族歴(突然死，肺高血圧症)，母体年齢，身長・体重，経妊・経産歴，高血圧，耐糖能異常の有無，妊娠中・分娩後の肺動脈圧の変化，右左心機能の変化。妊娠関連項目：分娩方法，分娩週数，出生体重。

### 2 統　計

連続変数で標準分布するものは，Student t-testで解析を行い，標準分布しないものはWilcoxon testを施行した。カテゴリアル解析を行う場合は$\chi^2$検定，Fisher's exact testを行った。

### 3 結　果

42名が42妊娠を行った(表1)。14例が軽症で28例が重症例であった。42名のうち，18名(軽症4名，重症14名)が妊娠初期に人工妊娠中絶を選択，または自然流産となった。肺高血圧症のカテゴリー分類は表3に示した。

### 4 原発性肺高血圧症

原発性肺高血圧症の患者は3例存在した。母体年齢は30，38，20歳(順に1985，2000，2003年の症例)であった。3名とも，労作時の疲労感，呼吸困難，浮腫が増悪し，妊娠25～30週にて紹介となった。入院時，患者の$PaO_2$レベルは75，66，86 mmHgであった。肺動脈圧は経胸壁心エコーで72/30，61/31，82/42 mmHgであった。来院時のNYHA class分類はⅣ，Ⅳ，Ⅲであった。帝王切開が全身麻酔下に32，28，32週に施行された。Swan-Ganzカテーテルを挿入し肺動脈圧を，橈骨動脈より動脈圧を測定し連続モニターを行った。PCPSが緊急時に備えて手術室内にいつでも使用できるように準備された。1985年における初回のケースにおいて母体死亡が発生した。胎児適応にて緊急帝王切開が施行されたが，気管内挿管後，血圧が低下し，PCPSを含む蘇生処置がなされたが，3日後に死亡した。その他の2例において母体は生存退院した。これら2例の母体予後がよかった点は肺高血圧症に対する薬剤治療によるところが大きいと考える。2003年の例においては分娩後浮腫が進行し，右心カテーテル検査で肺動脈圧は68/32 mmHgであった。心機能が重度に低下していたためにまず，ドブタミンが1 μg/kg/minで開始された。それにより歩行時の息切れなどの自覚症状が改善した。次にエポプロステノール持続静注療法が0.5 ng/kg/minで開始され，1週間に2回0.5 ng/kg/min増量し7 ng/kg/minまで増量した。治療中，患者は副作用として軽度の顎の痛みを訴えたが徐々に消失した。経胸壁エコー，右心カテーテル検査両者における肺高血圧は改善し，浮腫も改善し，患者は分娩12日後，エポプロステノール持続静注療法を継続し退院した。

### 5 重症と軽症の肺高血圧症の妊娠予後

分娩週数は二峰性の分布をとった(図2)。第1グループは30～32週にピークを示し，グレーで示す重症例で構成されていた。このなかにはEisenmenger症候群4人と特発性肺高血圧症5人が含まれ，重症例が90%以上を占めた。第2グループは妊娠37～38週にピークを持ち，ほぼ軽症例が占めた。第1グループのほとんどは喀血，全身倦怠感増強，下腿浮腫進行などの心不

表3 軽症・重症肺高血圧例における背景疾患

| Category | 軽症(n=14) | | 重症(n=28) | |
|---|---|---|---|---|
| | 流産(4) | 分娩(10) | 流産(14) | 分娩(14) |
| IPAH | 2 | — | 2 | 3 |
| 先天性心疾患 | 2 | 8 | 1 | 6 |
| ASD(pre/post-ope) | 1(0/1) | 3(1/2) | 1(0/1) | 1(0/1) |
| VSD(pre/post-ope) | 0 | 3(1/2) | 0 | 3(2/1) |
| PDA(pre/post-ope) | 1(0/1) | 1(1/0) | 0 | 2(0/2) |
| ECD(pre/post-ope) | 0 | 1(0/1) | 0 | 0 |
| Eisenmenger syndrome | — | — | 10* | 4* |
| ASD | | | 3 | 0 |
| VSD | — | — | 5 | 3 |
| PDA | | | 2 | 1 |
| 膠原病関連 | — | 2 | — | — |
| その他 | — | — | 1 | 1 |

ASD：atrial septal deffect, VSD：ventricular septal defect, PDA：patent ductus arteriosus, ECD：endocardial cushion defect, pre/post-ope：pre operation/post operation, IPAH：idiopathic pulmonary arterial hypertension。$\chi^2$ test と Fisher exact test で解析。*：$p<0.05$。

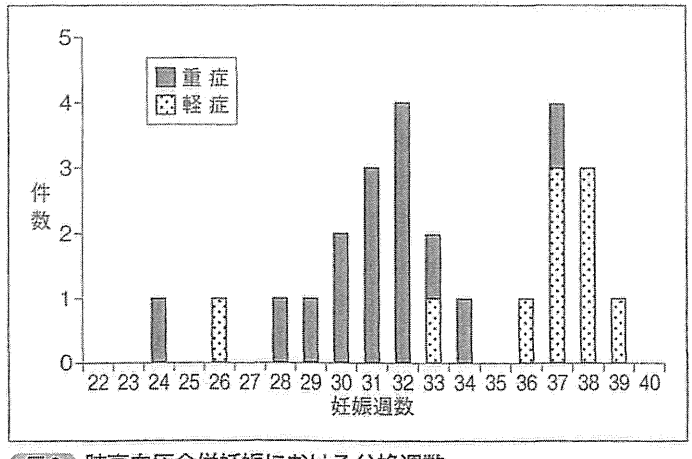


図2 肺高血圧合併妊娠における分娩週数
分娩週数は二峰性を示した。妊娠30～32週をピークとする主に重症例のグループと，妊娠37週以降の満期産でほぼ軽症例で構成されるグループ。前者は主に帝王切開での分娩，後者は主に経腟分娩の転機をとった。（文献32より引用）

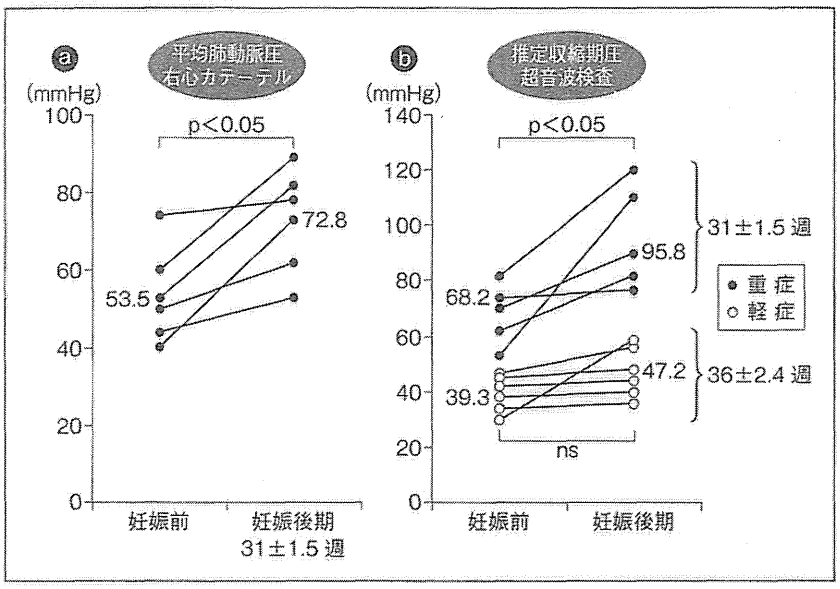


図3 妊娠中の肺動脈圧の変化

a：右心カテーテル検査による平均肺動脈圧。肺高血圧重症例では，妊娠前に比べて妊娠後期(平均妊娠31±1.5週)に有意に肺高血圧が上昇した(53.5±12.3 vs. 72.8±13.3 mmHg, $p<0.05$)。

b：経胸壁心エコー検査による肺動脈の推定収縮期圧。エコー検査でも，重症例は有意に肺高血圧は妊娠前と比較して妊娠後期(平均妊娠31±1.5週)に有意に肺高血圧は上昇した(68.2±11.1 vs. 95.8±18.5 mmHg, $p<0.05$)が，軽症例では上昇しなかった(39.3±6.6 vs. 47.2±9.2 mmHg, ns)。mean±SD。Student T testを用いた。 (文献32より引用)

全徴候を示し，Eisenmenger症候群においては$SpO_2$低下が特徴的であった。重症例のうち3例は急性の呼吸不全，3例で全身倦怠感と咳嗽，6例で肺高血圧の悪化，2例で自然陣痛発来し分娩に至った。重症例は軽症例に比べて分娩週数が有意に早く(31.5 vs. 35.4週，$p<0.05$)，出生体重は有意に軽かった(1,464±290 g vs. 2,543±350 g，$p<0.05$)。胎児発育に関しては重症例の8/15，57%が妊娠週数に比べて小さな発育をしていたが，軽症例では10/10，100%の胎児が週数相当の発育をした(表2)。

### 6 心エコー検査と右心カテーテル検査

今回，肺高血圧治療薬を使用した例は含めずに検討を行った。近年の3症例においては，肺高血圧合併妊娠やその予後について十分に説明した後，タダラフィル，エポプロステノールの2剤を妊娠第1期に導入し，妊娠第2期における循環動態の変化に備えた。そのような例においては子宮内胎児発育不全の児が少ない傾向にあった(0/3)。

重症例において平均肺動脈圧は右心カテーテル(53.5±12.3 vs. 72.8±13.3 mmHg，$p<0.05$)，心エコー(68.2±11.1 vs. 95.8±18.5 mmHg，$p<0.05$)による推定収縮期圧の2つの評価で妊娠週数が進むにつれて上昇した(図3)。軽症例では心エコーによる推定収縮期圧(39.3±6.6 vs. 47.2±9.2 mmHg，ns)(図3b)の有意な上昇はみられなかった(表4)。

### 7 NYHAクラス分類

軽症のPAH 10例のうち7例は，NYHAクラス分類Ⅰが全妊娠期間で変化しなかった(図4)。残りの3名は妊娠前にクラスⅡ，うち2名は分娩後までクラスⅡ，1名はクラスⅢに転じた。14名の重症例で妊娠前に，1名はクラスⅠ，

表4 軽症および重症肺高血圧症における妊娠初期のエコー検査成績

| | 軽症 (n=14) | 重症 (n=28) | p 値 |
|---|---|---|---|
| 収縮期肺動脈圧* | | | |
| 妊娠前 | 39.3±6.6 | 68.2±11.1 | <0.05 |
| 妊娠後期 | 47.2±9.2 | 95.8±18.5 | <0.05 |
| 三尖弁逆流 | | | |
| None-mild | 9 | 8 | <0.05 |
| Moderate-severe | 5 | 20 | |
| 肺動脈弁逆流 | 2 | 3 | ns |
| %FS | 36.5±5.6 | 37.5±4.6 | ns |
| 右房拡大 | 2 | 17 | <0.05 |
| 右室拡大 | 2 | 18 | <0.05 |

*：収縮期の肺動脈圧は妊娠初期・後期の変化を含む。$p<0.05$ で有意差ありとした。%FS，収縮期の肺動脈圧は Student t-test で解析し mean±SD で表示。その他のデータは $\chi^2$ test と Fisher exact test で解析した。

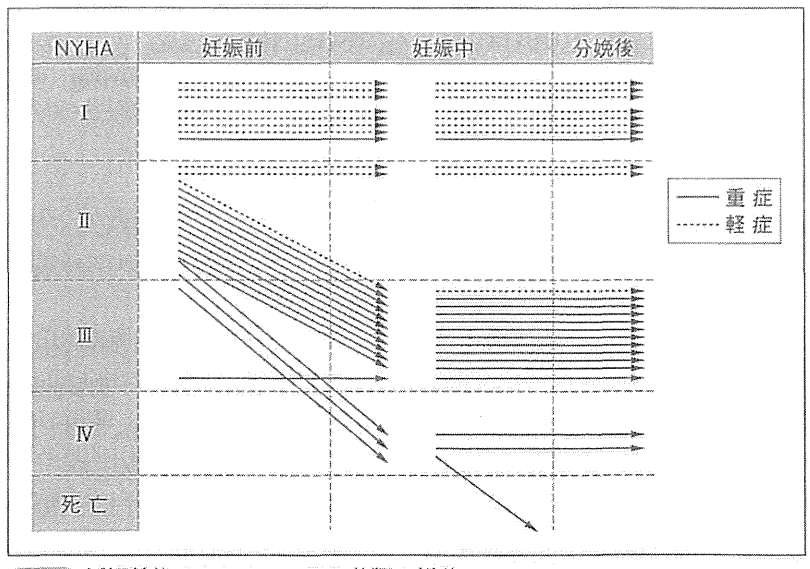


図4 妊娠前後の NYHA クラス分類の推移
軽症例では 10 例中 7 例が NYHA クラス分類Ⅰで推移，2 例はクラスⅡで推移，1 例はクラスⅡからクラスⅢへ転じた。重症例では妊娠前に 1 例がクラスⅠ，12 例がクラスⅡ，1 例がクラスⅢであり 2 例を除いて全例 NYHA クラスが妊娠中低下し，1 名が死亡した。（文献 32 より引用）

12名はクラスⅡ，1名はクラスⅢであった。2名以外，妊娠経過中NYHAクラス分類は悪化した。分娩中に1名の患者が気管内挿管後，血圧が低下し3日後に死亡，産褥期には11名はクラスⅢ，2名はクラスⅣに転じた。

## 2．考　察

肺高血圧症患者において妊娠中の肺高血圧の変化が記録された。重症例においては妊娠中，分娩時に肺高血圧が有意に上昇したが，軽症者では上昇しなかった。肺高血圧は重症例の全例で上昇した。肺高血圧患者においては肺血管が狭窄し，心拍出量も減少するので循環血液量の増加を伴う妊娠は許容できず，咳，労作時の呼吸不全，倦怠感が出現する。循環血液量は妊娠30週で非妊娠時の約140～150％に達し，その後一定である[36]。重症例では，この循環血液量増加を代償できず症候性となり，母体適応の分娩となったと考えられる。呼吸不全，労作時呼吸不全，下腿浮腫などが出現した。しかしながら，意外にも，不整脈や，狭心症症状は今回の症例では出現しなかった。これは妊娠を早めに中断したためと考えられる。

肺高血圧症における妊娠は60％にも上る高い母体死亡率が報告されているが，母体死亡は1例のみであった。これには，以下の3点が寄与していると思われる。1番目は重症例について，妊娠30週前後で妊娠の中断を行ったために母体の循環負荷が軽度に抑えられたことである。妊娠の早期中断はNICU医療の発展に支えられている。未熟性の高い1,000～1,500 gで出生した新生児全例が神経学的障害を残さず生存した。第2にベラプロスト，シルデナフィル，エポプロステノールなどの肺高血圧薬の導入である。第3は麻酔管理の進歩である。帝王切開中，特に，胎盤娩出後に肺動脈圧が体血圧を超えるときにはSwan-Ganzカテーテルから100 m*l*の血液を数分間で瀉血を施行，選択的に体血圧を上げるためにネヨシネジン0.2 mg ivを行うなどの高水準の麻酔管理が行われた。重症の肺高血圧を持つ女性は軽症の女性より不当軽量児(在胎週数に比べて体重が軽い)の頻度が高かった。これは心拍出量の減少による子宮血流量の低下に起因すると考えられる。しかしながら，重症の肺高血圧症より出生した，これらの児の発育，神経学的発達は良好であった。

軽症の肺高血圧症の多くは自然陣痛発来後に妊娠満期で経腟分娩を行い，妊娠による生理的な心拍数や循環血液量の増加を許容した。彼らは無症候で妊娠期間中，肺高血圧の上昇を認めなかった。これらの事実は軽症の肺高血圧症の女性においては厳重な管理を行えば妊娠は可能であることを示唆する。しかしながら，10例中8例の肺高血圧症の患者は先天性心疾患による肺高血圧症であり，原発性肺高血圧症の患者が少なく，原発性肺高血圧症の患者においてはさらなる研究が必要である。例えば，循環血液量が増加する以前からのエポプロステノールの持続静注や経口のシルデナフィルを用いた肺高血圧薬の投与などである[37]。そのためには妊娠前，あるいは妊娠初期に肺高血圧症を同定することも同時に重要な要素である。

## 3．結　論

肺高血圧の重症者においては妊娠期間中に肺高血圧は有意に上昇した。また帝王切開中に1例母体死亡が発生し，重症者においては妊娠後半期においてNYHAクラス分類はⅢ～Ⅳに低下した。ゆえに妊娠の早期中断が必要であり，不当軽量児の頻度が高かった。軽症の肺高血圧症は妊娠を許容すると考えられたが，10名中8名が先天性心疾患に起因する肺高血圧症であり，原発性肺高血圧症に関しては軽度であっても妊娠が安全かどうか，今後の検討が必要である。

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Med. Mycol. J.
Vol. 55E, E 1 – E 7, 2014
ISSN 2185 – 6486



Original Article

# Antifungal Susceptibility of *Candida* Isolates at One Institution

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## ABSTRACT

Species distribution and antifungal susceptibility of *Candida* isolates at one institution were evaluated. Detection rates of fungi were examined for 5 years between 2007 and 2011. Sensitivities of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole were evaluated in blood culture-positive patients. A total of 3,832 fungal isolates were detected, including *Candida albicans* 66.5%, *Candida glabrata* 20.3%, *Candida parapsilosis* 6.2%, *Candida tropicalis* 5.5%, and others 1.5%. Candidemia was diagnosed in 131 patients, and *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis*, and others were present in 42.0%, 27.5%, 16.0%, 8.4%, and 6.1% of these patients, respectively. Voriconazole had the lowest $MIC_{90}$s against *C. albicans* and *C. parapsilosis* (0.015 and 0.25). Micafungin had a low $MIC_{90}$ against *C. glabrata* and *C. tropicalis*. *C. albicans* was the most common fungus in patients with candidemia. Voriconazole and micafungin were effective against *C. albicans*. Amphotericin B was effective for *C. parapsilosis*, and micafungin showed good efficacy against *C. glabrata* and *C. tropicalis*.

Key words : fungus, antifungal susceptibility, antifungal agents, *Candida*, candidemia

## Introduction

Recent developments in medical technology have improved the survival of patients with severe tissue damage, those who undergo complex surgery, and those with severe circulatory failure. However, deep mycosis in these patients may induce opportunistic infections that may be difficult to diagnose and treat. The incidence of deep mycosis has increased in surgery, ambulatory care, and intensive care units, and is commonly treated with antimicrobial agents. *Candida* mycosis is treated with empirical therapy using azole antifungal drugs including fluconazole, and the prognosis is good. However, *Candida albicans* may show low sensitivity or resistance to these drugs, and non-*albicans Candida* species are also increasingly being isolated[1–5].

In this study, the detection rate of deep mycosis, the drug sensitivity of the causal species, and the use of antifungal drugs were examined at the National Cerebral and Cardiovascular Center (NCVC). The goals of the study were to establish the antifungal drug sensitivity of *Candida* strains isolated in the center and to identify appropriate agents for treatment of deep mycosis.

## Materials and Methods

The detection rates of fungi at the NCVC were determined for 5 years between January 2007 and December 2011. Sensitivities of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole were examined in blood culture-positive patients. The NCVC is located in

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Received : 6, March 2013. Accepted : 7, November 2013

Table 1. Yearly changes of species distribution of 3,832 fungi detected at the National Cerebral and Cardiovascular Center from 2007 to 2011

| Species | Number. of isolates | | | | | |
|---|---|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 | 2011 | Total (%) |
| *C. albicans* | 461 (70.4) | 457 (72.9) | 350 (65.2) | 555 (71.2) | 725 (58.8) | 2,548 (66.5) |
| *C. glabrata* | 128 (19.5) | 133 (21.2) | 119 (22.2) | 131 (16.8) | 265 (21.5) | 776 (20.3) |
| *C. parapsilosis* | 23 (3.5) | 24 (3.8) | 31 (5.8) | 46 (5.9) | 115 (9.3) | 239 (6.2) |
| *C. tropicalis* | 30 (4.6) | 12 (0.9) | 34 (6.3) | 36 (4.6) | 100 (8.1) | 212 (5.5) |
| *C. krusei* | 6 (0.9) | 1 (0.2) | 1 (0.2) | 2 (0.3) | 13 (1.1) | 23 (0.6) |
| *C. lusitaniae* | 1 (0.2) | — | — | 7 (0.9) | 11 (0.9) | 19 (0.5) |
| *C. guilliermondii* | 6 (0.9) | — | 2 (0.4) | 2 (0.3) | 5 (0.4) | 15 (0.4) |
| Total | 655 | 627 | 537 | 779 | 1,234 | 3,832 |

All data are shown as a number with the percentage for each year shown in parentheses.

an urban area in Japan, and specializes in surgical treatment of cardiovascular diseases, including cerebrovascular and internal injuries. The facility also manages pregnancy and delivery for women with maternal cardiac diseases. The NCVC has 612 beds and about 10,000 new hospital stays each year. The average hospital stay is 17 days, and 650 and 190 heart surgeries are performed annually for adults and infants, respectively. Ten heart transplantations are performed each year.

**Culture media**

CHROMagar Candida (CHROMagar, Paris, France) was purchased as a powder. CHROMagar is composed (per liter) of 10 g peptone, 20 g glucose, 15 g agar, 0.5 g chloramphenicol, and 2 g chromogenic mix. The medium was prepared according to the manufacturer's instructions and dispensed in petri dishes (20 m*l* in a 90-mm diameter dish).

**Identification of fungus species**

Clinical specimens from cases with suspected myconal infections were inoculated onto CHROMagar and incubated at 37℃ for 48 h. Macroscopic identification was performed based on the color and shape of the grown colonies. Strains without typical characteristics on the CHROMagar were identified with a ID 32℃ Yeast Identification System (bioMerieux S. A.), using colonies on the CHROMagar prepared using the solution provided with this system.

**Determination of sensitivity to antifungal drugs**

The microdilution method was used to study drug sensitivity, using an Antifungal Susceptibility Test for Yeast (Kyokuto Pharmaceutical Industrial Co.) that complied with Clinical and Laboratory Standards Institute (CLSI) criteria. M27-A3 was used to determine the minimum inhibitory concentration (MIC) of amphotericin B (measurable concentration range 0.03-16 μg/m*l*), flucytosine (0.125-64 μg/m*l*), fluconazole (0.125-64 μg/m*l*), micafungin (0.03-16 μg/m*l*), itraconazole (0.015-8 μg/m*l*), and voriconazole (0.03-16 μg/m*l*). Sensitive (S), sensitive dose-dependent (S-DD), intermediate (I), and resistant (R) responses to flucytosine, fluconazole, and itraconazole were evaluated using CLSI M27-S3 criteria[6].

The study was exempted from Committee on Human Research approval (National Cerebral and Cardiovascular Center) because there no longer exists a key or code sheet relating the individuals' identities to their private health information.

## Results

A total of 3,832 patients had a detected fungal infection in the 5-year period from 2007 to 2011 in the NCVC, including 2,548 patients with *C. albicans* (66.5%), 776 with *C. glabrata* (20.3%), 239 with *C. parapsilosis* (6. 2%), and 212 with *C. tropicalis* (5.5%) (Table 1). Non-*albicans* infections accounted for 33.5% of cases. The location and materials of isolated *Candida* species are shown in Table 2.

The number of blood culture performed were 2,819, 3,306, 2,900, 3,797, 4,239 in 2007, 2008, 2009, 2010, and 2011, respectively. The number and percentages of patients with fungemia caused by *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis, Candida lusitaniae, Candida guilliermondii*, and *Candida krusei* were 55 (42.0%), 36 (27.5%), 21

Table 2. Location and materials of isolated *Candida* species

| Species | Sputum | Urogenital | Stool | Intra-body material | Blood | Skin | Others | Total |
|---|---|---|---|---|---|---|---|---|
| C. albicans | 1,309 (72.8) | 800 (62.7) | 150 (56.0) | 113 (58.9) | 55 (42.0) | 81 (79.4) | 40 | 2,548 |
| C. glabrata | 291 (16.2) | 333 (26.1) | 87 (32.5) | 25 (13.0) | 21 (16.0) | 10 (9.8) | 9 | 776 |
| C. parapsilosis | 56 (3.1) | 77 (6.0) | 8 (3.0) | 38 (19.8) | 36 (27.5) | 11 (10.8) | 13 | 239 |
| C. tropicalis | 123 (6.8) | 49 (3.8) | 17 (6.3) | 11 (5.7) | 11 (8.4) | | 1 | 212 |
| C. krusei | 13 (0.7) | 4 (0.3) | 4 (1.5) | | 1 (0.8) | | 1 | 23 |
| C. lusitaniae | 4 (0.2) | 5 (0.4) | 2 (0.8) | 2 (1.0) | 5 (3.8) | | 1 | 19 |
| C. guilliermondii | 2 (0.1) | 8 (0.6) | | 3 (1.6) | 2 (1.5) | | | 15 |
| Total | 1,798 | 1,276 | 268 | 192 | 131 | 102 | 65 | 3,832 |

All data are shown as a number with the percentage in parentheses. Sputum includes respiratory related materials. Intra-body materials include catheters and drainage tube. Aspiration fluid indicates ascites, pleural effusion, and pericardial effusion.

Table 3. Yearly changes of species distribution of 131 *Candida* blood isolates detected at the National Cerebral and Cardiovascular Center from 2007 to 2011

| Species | Number (%) of isolates | | | | | |
|---|---|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 | 2011 | Total |
| *C. albicans* | 7 (41.1) | 7 (43.8) | 8 (44.4) | 25 (59.5) | 8 (25.0) | 55 (42.0) |
| *C. parapsilosis* | 2 (11.8) | 4 (25.0) | 3 (16.7) | 11 (25.0) | 16 (44.4) | 36 (27.5) |
| *C. glabrata* | 3 (17.7) | 3 (18.8) | 4 (22.2) | 5 (11.4) | 6 (16.7) | 21 (16.0) |
| *C. tropicalis* | 4 (23.5) | 1 (6.3) | 2 (11.1) | 2 (4.6) | 2 (5.6) | 11 (8.4) |
| *C. lusitaniae* | — | 1 (6.3) | — | 1 (2.3) | 3 (8.3) | 5 (3.8) |
| *C. guilliemondii* | 1 (5.9) | — | 1 (5.6) | — | — | 2 (1.5) |
| *C. krusei* | — | — | — | — | 1 (2.8) | 1 (0.8) |
| Total | 17 | 16 | 18 | 44 | 36 | 131 |

All data are shown as a number with the percentage for each year in parentheses.

(16.0%), 11 (8.4%), 5 (3.8%), 2 (1.5%), and 1 (0.8%), respectively (Table 3), with 58% of the cases of fungemia caused by a non-*albicans* species.

**Drug sensitivity**

Data for the sensitivity of fungi to amphotericin B, flucytosine, fluconazole, micafungin, itraconazole, and voriconazole are shown in Table 4. Amphotericin B was not classified into S, S-DD, I, and R categories in the CLSI 2009 criteria.

The $MIC_{90}$ of voriconazole against *C. albicans* (0.015) was the lowest among the 6 antifungal drugs, followed by micafungin (0.06), flucytosine (0.25), itraconazole (0.25), amphotericin B (0.5), and fluconazole (0.5). However, none of the 55 patients with candidemia caused by *C. albicans* showed resistance in the CLSI criteria (flucytosine $\geq$ 32, fluconazole $\geq$ 64, itraconazole $\geq$ 1, voriconazole $\geq$ 4). Of these 55 cases, 46 (83.6%) were S-DD to itraconazole and all 55 were sensitive to the other 5 antifungal drugs.

The $MIC_{90}$ of voriconazole and against *C. parapsilosis* (0.125) was also the lowest among the antifungal drugs, followed by flucytosine (0.25), amphotericin B (0.5), itraconazole (1), micafungin (2), and fluconazole (16). The resistance rates of *C. parapsilosis* to fluconazole and itraconazole were 5.6% and 25.0%, respectively. The percentages of patients with S ($\leq$ 0.125), S-DD (0.25–0.5), and R ($\geq$ 1) responses were 27.8%, 47.2%, and 25.0%, respectively, for itraconazole. The percentages of patients with S ($\leq$ 8), S-DD (16–32), and R ($\geq$ 64) responses were 83.3%, 11.1%, and 5.6%, respectively, for fluconazole.

The $MIC_{90}$ of micafungin against *C. glabrata*

Table 4. Antifungal susceptibilities of *Candida* blood isolates determined by microdilution method after 48 h of incubation

| Species (number of isolates) | Antifungal agent | MIC (μg/ml) [a] range | 50% | 90% | % Resistant[b] |
|---|---|---|---|---|---|
| *C. albicans* (55) | Amphotericin B | 0.13-1 | 0.5 | 0.5 | — |
| | Flucytosine | < 0.13-1 | 0.13 | 0.25 | 0 |
| | Fluconazole | < 0.13-2 | 0.25 | 0.5 | 0 |
| | Micafungin | < 0.03-0.06 | < 0.03 | 0.06 | — |
| | Itraconazole | 0.03-0.5 | 0.13 | 0.25 | 0 |
| | Voriconazole | < 0.015-0.5 | < 0.015 | 0.015 | 0 |
| *C. parapsilosis* (36) | Amphotericin B | 0.13-1 | 0.25 | 0.5 | — |
| | Flucytosine | < 0.13-0.5 | 0.25 | 0.25 | 0 |
| | Fluconazole | 0.5-64 | 1 | 16 | 5.6 |
| | Micafungin | 0.25-2 | 0.5 | 2 | — |
| | Itraconazole | 0.13-2 | 0.25 | 1 | 25 |
| | Voriconazole | < 0.015-1 | 0.03 | 0.125 | 0 |
| *C. glabrata* (21) | Amphotericin B | 0.13-1 | 0.5 | 1 | — |
| | Flucytosine | < 0.13-0.25 | < 0.13 | 0.13 | 0 |
| | Fluconazole | 8-> 64 | 16 | 64 | 19.1 |
| | Micafungin | < 0.03-0.06 | < 0.03 | 0.06 | — |
| | Itraconazole | 1-> 8 | 2 | 8 | 100 |
| | Voriconazole | 0.25-> 8 | 0.5 | 1 | 14.3 |
| *C. tropicalis* (11) | Amphotericin B | 0.13-1 | 0.25 | 0.5 | — |
| | Flucytosine | 0.13-4 | 0.25 | 0.25 | 0 |
| | Fluconazole | 1-> 64 | 8 | > 64 | 36.4 |
| | Micafungin | 0.06-2 | 0.06 | 0.13 | — |
| | Itraconazole | 0.25-> 8 | 4 | > 8 | 72.7 |
| | Voriconazole | 0.13-0.5 | 0.25 | 0.5 | 0 |

[a] 50% and 90% minimum inhibitory concentrations: $MIC_{50}$ and $MIC_{90}$, respectively.
[b] Percentage of resistant strains according to CLSI breakpoints (CLSI M27-S3 2009)
CLSI: Clinical and Laboratory Standards Institute; "-" indicates break point is not established in CLSI M27-S3

(0.06) was the lowest among the antifungal drugs, followed by flucytosine (0.13), amphotericin B (1), and voriconazole (1). The resistance rate to voriconazole was 14.3%. The drug resistance rates of itraconazole and fluconazole were 100% and 19.1%, respectively.

The $MIC_{90}$ of micafungin against *C. tropicalis* (0.13) was significantly lower than those for other drugs, followed by amphotericin B and voriconazole (both 0.5). The resistance rate of *C. tropicalis* against voriconazole was 0%.

## Discussion

131 *Candida* strains isolated from blood at the NCVC from 2007 to 2011 showed species distribution, *C. albicans* 42.0%, *C. parapsilosis* 27.5%, *C. glabrata* 16.0%, *C. tropicalis* 8.4%, and *C. krusei* 0.8%. Our data and the results of a national surveillance study indicate that *C. albicans* is still the major causal fungus of candidemia in Japan. In *C. albicans* no isolate with resistance to fluconazole $\geq$ 64 μg/ml was found in this study[7]. The 90%MIC was 0.5 μg/ml and the isolate with

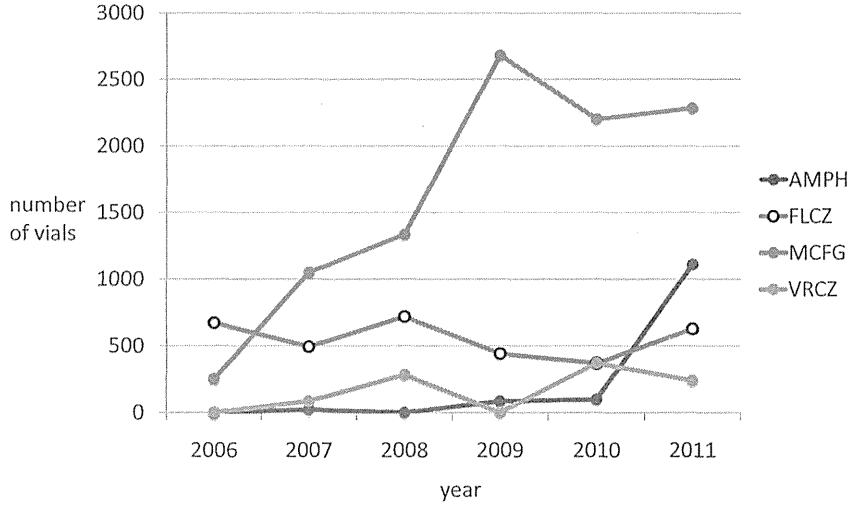


Fig. 1. Use of antifungal agents. Fluconazole was the most commonly used antifungal drug in 2006, whereas micafungin was most commonly used from 2007 to 2011. Use of AMPH increased in 2011, which reflects the increase of fungemia caused by *C. parapsilosis*. AMPH: amphotericin B, FLCZ: fluconazole, MCFG: micafungin, VRCZ: voriconazole.

lowest susceptibility required 2 μg/ml. These findings led us to use an antifungal susceptibility-based management strategy in NCVC for treatment for known *C. albicans* infection in which fluconazole is the first line antifungal drug.

The rates of resistance of *C. glabrata* to itraconazole and fluconazole (100% and 20%) were greater than those (56.3% and 5.2%) in Takakura et al[7]. High rates of resistance to itraconazole for *C. glabrata* detected in the bloodstream were also found by Myoken (100%, 8/8) [8] and St-Germain et al. (83.3%, 65/78) [9]. In our study, none of the 25 *Candida* isolates with reduced susceptibility to fluconazole (MIC $\geq$ 16 μg/ml) was susceptible to itraconazole (MIC $\leq$ 0.12 μg/ml). However, Pfaller et al. suggested that MICs of $\leq$ 1 μg/ml may better reflect 'susceptibility' in invasive candidiasis, due to the higher serum concentrations achievable with the new nanocrystal intravenous formulation of itraconazole[10]. Given this new threshold, 40.0% of our isolates with reduced susceptibility to fluconazole would be considered susceptible to itraconazole. Furthermore, our observations are similar to those of Pfaller et al., with all four of our *C. glabrata* isolates that were resistant to fluconazole also showing resistance to itraconazole.

The higher resistance rate of *C. tropicalis* to fluconazole (36.4%) compared to reports from the USA (6.2%) and Spain (16.6%) is another characteristic of non-*albicans* candidemia in this study[11, 12]. We attribute this high resistance to the consistent and high frequency use of fluconazole in our facility. Interestingly, for each case of fluconazole-resistant non-*albicans* candidemia (4 isolates of *C. glabrata*, and 4 isolates of *C. tropicalis*), micafungin showed high sensitivity and can be regarded as the first choice for treatment of fluconazole-resistant *C. glabrata* and *C. tropicalis*. Voriconazole showed no resistance to *C. tropicalis* and may be used as the second choice for these isolates in our hospital; however, voriconazole showed a resistance rate of 43.5% in a national survey[7]. This discrepancy suggests that the susceptibility of each species of *Candida* differs from hospital to hospital, due to the different disease backgrounds and treatments at each center. This indicates that antifungal drug susceptibility at each facility should be considered in the selection of antifungal drugs.

In this study, the greatest number of fungi in the bloodstream was detected in 2011 and the incidence of the disease caused by *C. parapsilosis* (n = 16) was the highest in the same year. The incidence of candidemia caused by *C. albicans* gradually decreased in the study period. We attribute this increase of *C. parapsilosis* to the increase in operations for candidates for heart transplantation and for neonates with congenital heart diseases. These immunologically compromised patients underwent treatments including central line management, which is a known risk

factor for *C. parapsilosis*. This increase in *C. parapsilosis* caused a temporary increase in use of amphotericin B in 2011 (Fig. 1). The selection of this drug for *C. parapsilosis* has turned out to be appropriate because in this study fluconazole showed a resistance rate of 5.6% and a $MIC_{90}$ with micafangin that was as high as 2.0 $\mu$g/ml. The $MIC_{90}$ of voriconazole was 0.125, which makes this drug the second choice for *C. parapsilosis* in the NCVC.

We introduced micafungin for treatment of deep mycosis in 2004. By 2006, micafungin accounted for 27% of all antifungal drugs used in the NCVC and from 2009 to 2011 this rate reached 70%. This increased use has occurred because micafungin is an echinocandin that has a broad antifungal spectrum and exhibits good activity against azole antifungal drug-resistant strains. Micafungin is effective in fungal cell lines and several reports have shown excellent tissue penetration and clinical effects[13, 14]. Thus, micafungin has been most commonly used at the NCVC since 2007, including preservational use for immunocompromised patients, such as those undergoing cardiac transplantation or in extremely low-birthweight infants in the NICU. However, several clinical isolates of *Candida* with low resistance to echinocandin antifungal drugs have been described and care is taken regarding this issue at the NCVC[15–18]. The mechanism of this reduced sensitivity involves a mutation in Fkslp, which is a 1,3$\beta$-D-glucan synthase subunit of the target enzyme of echinocandins[15–18]. No strains with reduced sensitivity to micafungin were found in this study. However, as clinical use of the drug continues to increase, particular attention should be paid to the sensitivity of clinical isolates to micafungin.

*C. lusitiniae* is an infrequent cause of fungemia, but the rate obtained in this study (3.8%) was 6.8 times higher than that in Takakura[7] and Minari et al[19]. The reported underlying conditions for patients with deep seated *C. lusitaniae* infections are malignancy 53%, neuropenic 35%, receiving broad-spectrum antibiotics 27%, receiving long-term corticosteroid therapy 16%, and having a central venous catheter 27%[20]. Although fungemia is the most common type of *C. lustaniae* infection (80%), primary infection focuses were identified in 20% of cases[20]. These included endocarditis, infection of a left ventricular device, meningitis, chorioamnionitis, peritonitis, abdominal abscess, and cutaneous infection, and most of these diseases are treated at our center. These facts may be related to the higher detected rate of *C. lustaniae* fungemia at our institution. *C. tropicalis* and *C. krusei* are likely to cause deep mycosis in patients with hematologic tumors undergoing digestive tract surgery, but this type of surgery is not performed at the NCVC. This may explain the low incidence of fungemia at the NCVC due to these species[2–4].

In summary, it is important to comprehend the susceptibility for antifungal drug and distribution of each *Candida* isolate of each hospital in selection of antifungal drug, due to the different disease backgrounds and treatments at each center.

**Limitations**

The sample population was small in this study. In particular, only 11 patients had *C. tropicalis*, which is the minimum required to calculate MIC, and further validation of this result is required. Drug sensitivity may vary depending on the actual treatment in medical institutions, in particular regarding use of the antifungal drug. The NCVC is a specialized center for internal medicine and cardiovascular surgery in patients with cardiovascular disorders or cerebrovascular accident, in contrast to the roles of secondary or tertiary hospitals for general patients. Therefore, it is important to study the drug sensitivity of fungi and measures to be taken against infections in centers such as the NCVC, in which immunocompromised patients are treated, including those undergoing cardiac transplantation, even if the study population is small.

## Acknowledgments

The authors thank all the nursing staff at the NCVC for their clinical assistance.

**Conflict of Interest Statement**

None of the authors has a conflict of interest regarding the work in this study.

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# Pregnancy-associated Intracranial Hemorrhage: Results of a Survey of Neurosurgical Institutes across Japan

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*Background:* Pregnancy-associated hemorrhagic stroke is considered a serious complication. Although coagulopathy, pregnancy-induced hypertension, eclampsia, and other systemic complications have been emphasized, pre-existing cerebrovascular diseases (CVDs) have not been fully analyzed. To clarify the role of these vascular lesions more in detail, the Japan Neurosurgical Society conducted a nationwide survey on all the neurosurgical institutes across Japan. *Methods:* This 2-year survey focused on hemorrhagic stroke occurring in pregnancy, delivery, and puerperium. Clinical data based on retrospective chart review were obtained through a questionnaire and analyzed according to the time of onset, underlying CVDs, obstetric systemic complications, therapeutic approaches, and maternal and neonatal prognoses. *Results:* The survey identified 97 hemorrhagic strokes that were associated with pregnancy. Baseline CVDs responsible for hemorrhage were detected in 54 cases (55.7%), among which 47 lesions (87.0%) had been undiagnosed before stroke onset. The detection rate of baseline CVDs before the 32nd week of gestation was significantly higher than that after the 32nd week (90.0% versus 53.3%, $P = .0017$). Arteriovenous malformations (AVMs) were the most frequent CVDs causing intracranial hemorrhage, occurring at 1.8 times the frequency of ruptured aneurysms during pregnancy. Poor outcomes, including 10 deaths, were seen in 36.1% of the cases despite aggressive treatment. *Conclusion:* Pregnancy-associated hemorrhagic strokes frequently concealed baseline CVDs, especially when they occurred before the 32nd week of gestation. AVMs were the predominant bleeding source. For appropriate treatment, therefore, close examination for cerebral vascular lesions is essential when a pregnancy-associated hemorrhagic stroke is encountered. **Key Words:** Pregnancy—stroke—intracranial hemorrhage—arteriovenous malformation—cerebral aneurysm—moyamoya disease.


## Introduction

Pregnancy-associated hemorrhagic stroke is well recognized as a serious complication.[1,2] In previous studies conducted mainly by neurologists and obstetricians, systemic obstetric complications including coagulopathies, pregnancy-induced hypertension, and eclampsia were identified as the causes of hemorrhage.[2-7] Pre-existing cerebrovascular diseases (CVDs) such as cerebral aneurysms and arteriovenous malformations (AVMs) were also reported,[4,8] but their incidence and treatments were not fully analyzed. The Japan Neurosurgical Society, therefore, set out to conduct a survey of neurosurgical institutes across Japan regarding pregnancy-associated hemorrhagic stroke with a special focus on identifying underlying CVDs.

## Methods

This study is a retrospective analysis based on the clinical chart review in each neurosurgical institute and was

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Received June 26, 2013; revision received August 6, 2013; accepted August 21, 2013.

**Grant support:** None.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2013.08.017

conducted in 2 phases (primary and secondary surveys) in 2012 as an official project of the Japan Neurosurgical Society. The society has 109 main training institutes across Japan under which 755 affiliated local training institutes participate in providing neurosurgical services. The target of the primary survey was all strokes occurring during pregnancy, delivery, and puerperium (no later than 6 weeks after delivery) that were treated in these institutes between January 2010 and December 2011. In the primary survey, all 109 main training institutes were assigned to compile the number of pregnancy-associated strokes treated in their own hospitals or affiliated local training institutes during the earlier mentioned period. The results were e-mailed to the survey office without any clinical information, and only the e-mail address of the corresponding physician in each case was provided. In the secondary survey, a questionnaire requesting detailed clinical information on each case was e-mailed to each corresponding physician and returned to the survey office without any personally identifying information attached. The clinical information included stroke type and time of stroke onset (gestational age or time after delivery), causes of hemorrhage, types of underlying CVDs, types of obstetric systemic complications, therapeutic procedures for strokes, methods of delivery, and maternal and neonatal prognoses.

Feedback on the primary survey was obtained from 102 (93.6%) main training institutes covering 729 affiliated local training institutes. The survey office sent secondary survey questionnaires to the 126 attendant physicians who had declared their experience with pregnancy-associated stroke and received feedback from 100 physicians (79.4%). After determining the eligibility of each case and eliminating duplications resulting from patient transfer between institutes, the authors extracted 134 cases. These strokes were divided into 97 hemorrhagic strokes (intracerebral or subarachnoid hemorrhage) and 37 other strokes (eg, cerebral arterial infarction or venous infarction), and the former 97 cases were submitted for the further analysis. Intracranial hemorrhage was confirmed by computed tomography (CT) or magnetic resonance (MR) imaging in all cases, and bleeding sources were further examined by MR angiography, digital subtraction angiography, or CT angiography except for a few cases of early death that could not allow further examinations.

### *Statistical Methods*

The data were presented as frequency or means within a standard deviation. Fisher exact probability test and Mann–Whitney *U* test were applied to categorical data. All analyses were performed with Statcel 3 software (OMS Publishing, Inc., Tokorozawa, Japan). Prognosis of the patients was expressed with the modified Rankin Scale (mRS)[9] at discharge.

**Table 1.** *Demographics of patients with pregnancy-associated hemorrhagic stroke*

| | n = 97 (100%) |
|---|---|
| Mean age (y) | 32.2 ± 5.4 |
| Timing of onset | |
| During pregnancy | |
| Number of cases | 60 (61.9%) |
| Mean gestational age at onset (wk) | 27.7 ± 10.1 |
| At delivery | |
| Number of cases | 13 (13.4%) |
| Mean delivery weeks | 38.4 ± 3.7 |
| Puerperium | |
| Number of cases | 24 (24.7%) |
| Time after delivery | |
| <24 h | 8 |
| 1-3 d | 4 |
| 3-7 d | 3 |
| 8-42 d | 8 |
| Unknown | 1 |

## Results

### *Patient Demographics*

Table 1 summarizes the patient demographics. Among the all 97 hemorrhagic strokes, 60 (61.9%) occurred during pregnancy, 13 (13.4%) at delivery, and 24 (24.7%) during puerperium. Mean gestational age at the onset of hemorrhage during pregnancy was 27.7 ± 10.1 weeks.

### *Causes of Hemorrhage in Each Period*

Figure 1, A shows the causes of hemorrhagic stroke throughout all periods (pregnancy, delivery, and puerperium). Baseline CVDs responsible for hemorrhage were detected in 54 cases (55.7%). Among all vascular lesions, AVMs are the most frequent cause of hemorrhage, followed by cerebral aneurysms and moyamoya disease. Another 3 lesions were also detected, including 2 cavernous malformations and 1 hemorrhage from the vasculature of an intraparenchymal tumor. Of all the detected CVDs, only 7 lesions (13.0%) had been diagnosed before pregnancy, and 47 lesions (87.0%) including all the aneurysms, 92.0% of AVMs, and 60.0% of moyamoya diseases had remained undiagnosed before stroke onset. Fourteen obstetric complications were identified, including pregnancy-induced hypertension, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, eclampsia, and disseminated intravascular coagulation. Because 2 of these complications were accompanied by bleeding from the AVM and moyamoya disease, they were categorized as "baseline CVDs," and the other 12 cases were categorized as "obstetric complication" in Figure 1. The cause could not be determined in 31 cases (32.0%). Figure 1, B illustrates the causes of hemorrhage in each period. The CVD detection rate was

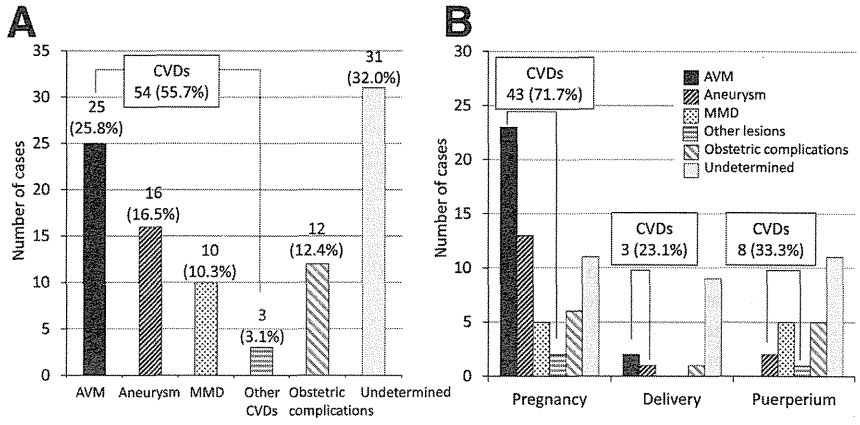


**Figure 1.** *(A) Causes of hemorrhagic stroke throughout all periods (pregnancy, delivery, and puerperium). (B) Causes of hemorrhagic stroke in each period. Abbreviations: AVM, arteriovenous malformation; CVDs, cerebrovascular diseases; MMD, moyamoya disease.*

71.7% for hemorrhage during pregnancy, 23.1% at delivery, and 33.5% during puerperium. Twenty-three of 25 AVM ruptures (92.0%) were detected during pregnancy, and none were detected during puerperium. Aneurysmal rupture occurred in all periods, but 13 of 16 ruptures (81.3%) were detected during pregnancy. All 6 hemorrhages related to obstetric complications were seen after the 32nd week of gestation.

### *Gestational Age at Onset and Cause of Hemorrhage during Pregnancy*

Figure 2 shows the gestational age at onset of hemorrhagic stroke during pregnancy. Hemorrhagic strokes remarkably increased in number at a later gestational age. Although hemorrhagic strokes before and after the 32nd week of gestation were equal in number (30 cases each), the detection rate of baseline CVDs reached 90.0% (27 of 30) before the 32nd week of gestation, which was significantly higher than that after the 32nd week (53.3%, $P = .0017$ in Fisher exact probability test). Hemorrhagic stroke without baseline CVDs occurred significantly later than that with CVDs (mean 33.7 ± 8.7 weeks versus 25.3 ± 9.6 weeks, respectively; $P < .001$ in Mann–Whitney $U$ test).

Figure 3 compares AVMs and cerebral aneurysms in terms of the gestational age at the onset of hemorrhage. The mean ages at the onset of AVM rupture and aneurysmal rupture were 24.6 ± 9.2 and 27.4 ± 10.4 weeks of gestation, respectively. More specifically, 13 of the 23 AVM ruptures (56.5%) occurred during the latter half (after the 22nd week) of pregnancy, whereas 10 of the 13 aneurysmal ruptures (76.9%) occurred during that same period. Although not statistically significant, aneurysmal rupture had a greater tendency to occur during the latter half of pregnancy than did AVM rupture ($P = .195$, Fisher exact probability test).

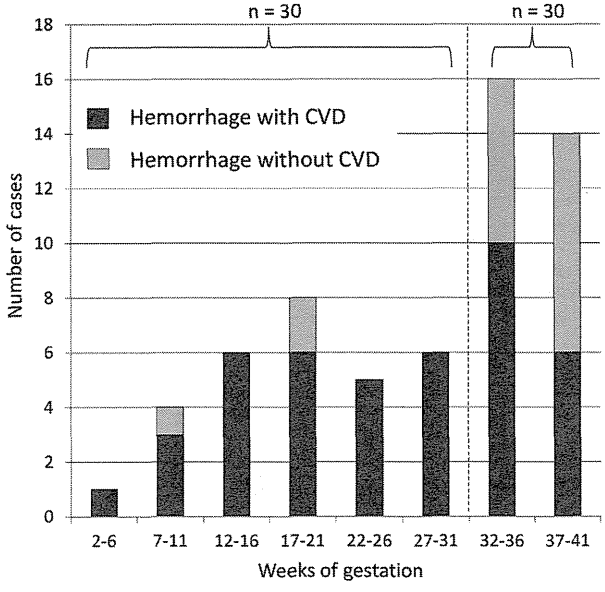


**Figure 2.** *Distribution of hemorrhagic strokes with and without determined baseline. CVDs by gestational age at onset. Abbreviation: CVD, cerebrovascular disease.*

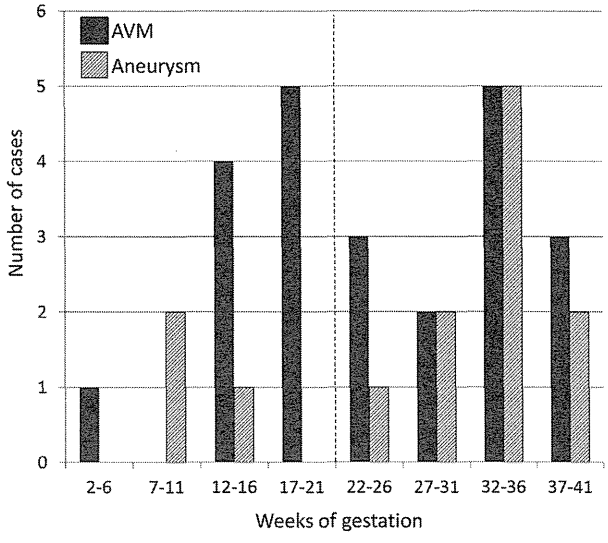


**Figure 3.** *Distribution of hemorrhagic strokes caused by AVMs and aneurysms by gestational age at onset. Abbreviation: AVM, arteriovenous malformation.*

**Table 2.** *Therapeutic approaches for pregnancy-associated hemorrhagic stroke*

| | | |
|---|---|---|
| AVM (n = 25) | | |
| Emergent surgery | 15 | |
| Nidus removal | | 8 |
| Hematoma removal | | 6 |
| Ventricular drainage | | 1 |
| Delayed surgery (nidus removal) | 2 | |
| Surgery in unknown period (nidus removal) | 2 | |
| Embolization in unknown period | 1 | |
| Nonsurgical treatment | 4 | |
| Unknown | 1 | |
| Aneurysm (n = 16) | | |
| Emergent neck clipping | 11 | |
| Emergent embolization | 4 | |
| None (dead on arrival) | 1 | |
| Moyamoya disease (n = 10) | | |
| Emergent surgery | 3 | |
| Hematoma removal | | 1 |
| Ventricular drainage | | 2 |
| Nonsurgical treatment | 7 | |
| Other CVDs (n = 3) | | |
| Emergent hematoma removal | 1 | |
| Nonsurgical treatment | 2 | |
| Hemorrhage without baseline CVDs (n = 43) | | |
| Emergent surgery | 16 | |
| Hematoma removal | | 10 |
| Ventricular drainage | | 6 |
| Nonsurgical treatment | 27 | |

Abbreviations: AVM, arteriovenous malformation; CVDs, cerebrovascular diseases.

### *Therapeutic Approaches and Modes of Delivery*

Table 2 summarizes the therapeutic approaches applied to hemorrhagic stroke. Among all cases, 55 (56.7%) required surgical treatment (direct surgery or endovascular surgery) and at least 50 (51.5%) were performed emergently. Eight of 25 AVMs were emergently removed by craniotomy, whereas in the other 7 cases hematoma removal or ventricular drainage was performed without nidus resection. All the aneurysms were emergently clipped or embolized except for 1 case found to be dead on arrival.

Figure 4 shows the methods of delivery adopted in 60 cases of hemorrhagic stroke during pregnancy. Before the 22nd week, induced abortion was selected in 36.8% of the cases, whereas gestation was continued until the elective delivery in 52.6%. When hemorrhage occurred after the 32nd week, 90% of the patients underwent emergent delivery, 96.3% of which were carried out by cesarean section.

### *Clinical Outcomes of Patients and Children*

Figure 5 illustrates the maternal clinical outcomes. Poor outcome (mRS score at discharge ≥ 3) was observed in 35 patients (36.1%). Fatal cases totaled 10,

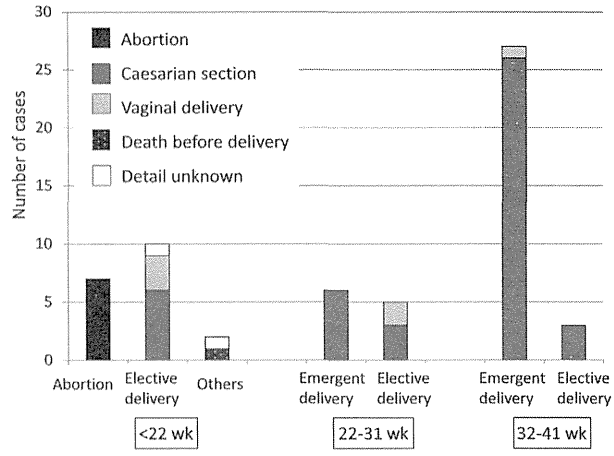


**Figure 4.** *Methods of delivery adopted after the onset of hemorrhagic stroke during pregnancy.*

making the mortality rate to be 10.3%. Hemorrhage without baseline CVDs showed a higher rate of poor outcome (mRS score ≥ 3) than did that associated with detected CVDs (41.9% and 32.1%, respectively), but the difference was not statistically significant ($P$ = .22, Fisher exact probability test).

Analysis of the prognosis for the children revealed that 81 (83.5%) were normal, whereas 1 (1.0%) had some sequelae and 1 (1.0%) died with the mother. There were 8 cases of abortion (8.2%): 7 were forced abortions after stroke at an early gestational age and 1 was an elective abortion followed by a fatal hemorrhage within 24 hours postpartum. Prognosis of 6 (6.2%) children was not reported.

## Discussion

Pregnancy-associated intracranial hemorrhage is a rare but potentially devastating event. A large population-

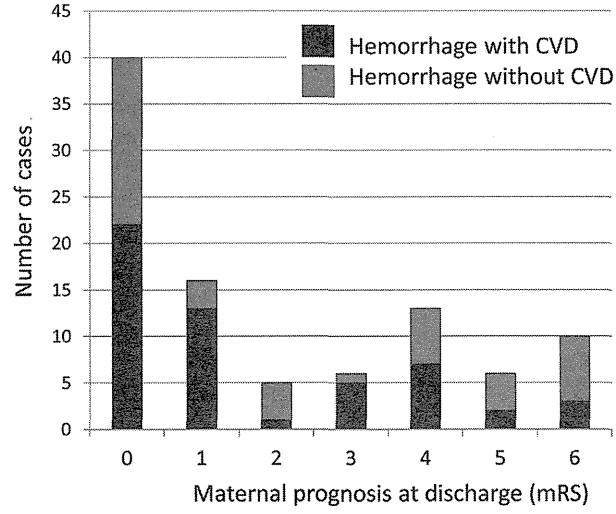


**Figure 5.** *Maternal outcomes after hemorrhagic stroke with and without determined baseline CVDs. Abbreviations: CVD, cerebrovascular disease; mRS, modified Rankin Scale.*

**Table 3.** *Recent studies on pregnancy-associated hemorrhagic stroke*

| Reference | Country | Total number | Causes of hemorrhage | | | | | Rate of CVDs (%) |
|---|---|---|---|---|---|---|---|---|
| | | | AVM | AN | MMD | Other CVDs | No CVD | |
| Simolke et al[13] | United States | 6 | 1 | 1 | 0 | 0 | 4 | 33.3 |
| Sharshar et al[12] | France | 16 | 2 | 2 | 0 | 2 | 10 | 37.5 |
| Kittner et al[5] | United States | 14 | 3 | 0 | 0 | 0 | 11 | 21.4 |
| Witlin et al[14] | United States | 6 | 1 | 2 | 0 | 0 | 3 | 50.0 |
| Jaigobin et al[8] | Canada | 13 | 5 | 3 | 0 | 0 | 5 | 61.5 |
| Witlin et al[15] | United States | 5* | 1 | 0 | 0 | 0 | 4 | 20.0 |
| Jeng et al[4] | Taiwan | 22 | 5 | 3 | 0 | 0 | 14 | 36.4 |
| Liang et al[1] | Taiwan | 21 | 4 | 2 | 0 | 0 | 15 | 28.6 |
| Scott et al[7] | United Kingdom | 12 | 1 | 3 | 0 | 0 | 8 | 33.3 |
| Present series | Japan | 97 | 25 | 16 | 10 | 3 | 43 | 55.7 |

Abbreviations: AN, aneurysm; AVM, arteriovenous malformation; CVDs, cerebrovascular diseases; MMD, moyamoya disease.
*Confined to postpartum stroke.

based epidemiologic study in Sweden conducted by retrospective *International Classification of Diseases, Ninth Revision,* code analysis revealed its incidence to be 6.2 (2.4 for subarachnoid hemorrhage and 3.8 for intracerebral hemorrhage) per 100,000 deliveries.[10] A more recent survey in the United States also based on the *International Classification of Diseases, Ninth Revision,* codes reported the incidence of intracerebral hemorrhage to be 6.1 per 100,000 deliveries.[11] In the study in Taiwan, on the other hand, much higher incidence has been reported (31.4 per 100,000 deliveries for all the intracranial hemorrhage).[1]

Causes of the hemorrhage emphasized in the previous studies have been rather different between one and another. In the earlier mentioned survey in the United States, various risk factors including pre-eclampsia/eclampsia, hypertension, and coagulopathy were pointed out and emphasized,[11] but the pre-existing CVDs were not analyzed in detail. A study from France particularly emphasized eclampsia that accounted for 44% of intracerebral hemorrhage although rupture of vascular lesions was found in 37%.[12] Several studies have described CVDs as the cause of hemorrhage, with the detection rate ranging from 21.4% to 61.5% (Table 3), but CVDs were not analyzed deeply, presumably because of the scarcity of such cases in these studies.[1,4,5,7,8,12-15] To the authors' knowledge, the present study of 97 cases is the first to undertake detailed analysis of baseline CVDs in pregnancy-associated stroke.

This study has revealed 2 important findings: first, hemorrhagic stroke conceals baseline CVDs at high frequency, especially before the 32nd week of gestation, and most had not been diagnosed until the bleeding had occurred. It can also be said that CVD-unrelated hemorrhages caused by obstetric complication or unknown etiology occur significantly later than those related to CVDs. The cause of this phenomenon has not been proven, but it is likely that the remarkable physiological changes occurring in late gestation are related to the increase in CVD-unrelated hemorrhage. As to the absolute CVD detection rate, the authors must clearly acknowledge the possibility of inclusion bias: this being a survey of neurosurgical institutes, it is possible that hemorrhagic cases diagnosed as having CVDs in the previous hospital could have been transferred selectively. An examination of the patient transfer state, however, revealed that 55.0% of the pregnant patients with intracranial hemorrhage were directly admitted in the surveyed institutes and that 36.7% had been transferred from the obstetric institution immediately after the diagnosis of hemorrhage without advanced examination of cerebral vascular lesions. This indicates that a total of 91.7% of our cases were free from this bias. Another highly possible bias is that patients with mild hemorrhage were treated by obstetricians or neurologists without a neurosurgeon being consulted and were thus excluded from the present study. Although there has been no evidence that severe hemorrhages are likely to be accompanied with CVDs and mild ones are not, the authors must admit the limitation of the present study with regard to this point. Accordingly, it might be proper to discuss the significant difference in CVD detection rate between the period before and the period after the 32nd week, rather than to argue the absolute value itself. At any rate, it is essential that patients presenting with intracranial hemorrhage during pregnancy be carefully examined for underlying CVDs.

The second novel finding is that AVMs are the predominant bleeding source, being 1.8 times more frequent than cerebral aneurysms during pregnancy. In the general population, AVM rupture is approximately one tenth as frequent as aneurysmal rupture[16,17]; even when confined to young adults, it is still one third as frequent as bleeding from an aneurysm.[18] These findings strongly suggest that physiological changes during pregnancy have a significant impact on the vasculature of AVMs, and ruptures during pregnancy are by no means coincidental. A review of the literature by neurosurgeons once

counted the number of past cases of pregnancy-related hemorrhage from aneurysms and AVMs and described the predominance of aneurysms compared with AVMs (77% versus 23%, respectively),[19] but these data were compiled from different countries and times and included many old case reports before the CT era. Recently, several studies showed the predominance of vascular malformations as shown in Table 2.[1,4,5,8] The small number of cases, however, precluded a robust conclusion about their prevalence. The present survey has clearly disclosed the predominance of AVMs at least in the Japanese population. Because no study proves a higher prevalence of AVMs in Asians than in Caucasians, the authors believe that this predominance is also applicable to Western populations.

All the aneurysms in the present series were emergently clipped or embolized except for 1 case found to be dead on arrival. This strategy apparently follows the recent recommendation that ruptured aneurysms should be managed in the same way as in the nonpregnant population.[19-21] Management of ruptured AVMs during pregnancy, on the other hand, has not yet been discussed in depth. Unlike cerebral aneurysms, AVMs exhibit a wide diversity in their amenability to surgical resection, from small resectable lesions in a noneloquent cortex to huge, deep-seated ones that cannot be removed.[17,22] Consequently, various surgical approaches were applied in the present study, including emergent nidus resection, ventricular drainage, and hematoma removal leaving the nidus unresected. The authors believe that ruptured AVMs should also be managed in the same manner as they are in the nonpregnant population, even during gestation. The mode and timing of surgery should be determined according to the size and location of the nidus, anatomical pattern of drainage, and volume of the intracerebral hematoma.[17,22]

This survey detected 10 hemorrhages caused by moyamoya disease, which accounted for 10.3% of all cases. Recently, pregnancy-associated stroke in moyamoya disease was closely studied in Japan, and the significance of both ischemia and hemorrhage has been emphasized.[23] The authors believe that the findings regarding moyamoya disease are applicable at least to other Asian countries.

A poor prognosis was identified in 36.1% of all the cases, with mortality reaching 10.3% despite aggressive treatment. This raises the question of whether it is possible to avoid these tragedies. Pre-existing CVDs, as described earlier, play a significant role in pregnancy-associated hemorrhagic stroke, and most remain undiagnosed until stroke onset. Certainly, nonpreventable strokes can occur in the absence of CVDs. Some obstetric complications might also be unavoidable. Clearly, however, one key to prevent a tragic hemorrhage is to detect the underlying CVDs before gestation. A routine brain checkup with MR angiography before pregnancy might reveal these lesions, but implementing such a strategy is not realistic from the viewpoints of medical economics, social and ethical issues surrounding marriage, and morbidity resulting from therapeutic intervention for CVDs that have remained asymptomatic. The familial occurrence of cerebral aneurysms, however, is well recognized, although most AVMs are sporadic.[24,25] The incidence of familial intracranial aneurysms (at least 2 affected first-degree relatives in the same family) among the patients of subarachnoid hemorrhage is 6%-10%,[26-28] and the relative risk for cerebral aneurysms among first-degree relatives in familial intracranial aneurysms families has been reported to be 4.2.[24] Moyamoya disease is also known to have genetic components,[29] and a lot of highly aggregated families with moyamoya disease has been reported.[30] Therefore, it should not be unreasonable to consider a medical checkup with brain MR angiography, at least for women anticipating pregnancy who have dense familial history. Although much discussion is needed, a poor maternal prognosis demands that we continue to address ways to prevent tragic pregnancy-associated strokes.

## Conclusions

A nationwide survey revealed that underlying CVDs play an important role in hemorrhagic stroke associated with pregnancy, among which AVM is the predominant bleeding source. Careful examination for vascular lesions is, therefore, essential when dealing with intracranial hemorrhage, especially before the 32nd week of gestation. As maternal prognosis after hemorrhagic stroke has been proved to be poor, a greater effort should be made to prevent tragic pregnancy-associated stroke.

**Acknowledgment:** The authors express their appreciation to Ms Kayoko Morii (secretary of the Department of Neurosurgery, Graduate School of Medicine, Kyoto University) for her great assistance in conducting the survey.

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