かん薬投与と比較して3歳時点での認知機能障害のリスクが高かった[16].

抗てんかん薬については，その催奇形性がよく知られている．このうちバルプロ酸については，児に二分脊椎をはじめとした様々な形態異常の増加をもたらすことが知られている[17]．通常妊娠を希望する女性に対しては第一選択薬として使用すべきでないとされているが，本論文はその方針を支持するものとなっている．さらに，催奇形性があまりにも有名なために，そこにばかり注目が集まるが，実地臨床においてはこうした児の生後発達についての考慮も必要であることを示しているといえよう．

妊娠とメトクロプラミド・妊娠と抗ヘルペス薬

メトクロプラミドは妊娠悪阻に対する制吐薬として汎用されている．従来から児の形態異常発生のリスクは上昇せず，その他の妊娠予後の悪化も認められないと考えられてきたが，2009年にこれまでで最大のコホート研究がイスラエルから発表された[18]．それによると，妊娠第一三半期にメトクロプラミド投与を受けた3458名の妊娠女性において，やはり児の形態異常，低出生体重，早産，周産期死亡の有意な増加は認められなかった．

一方，抗ヘルペス薬であるアシクロビルやバラシクロビルも催奇形性は否定的と考えられてきた医薬品であるが，2010年に大規模なコホート研究が発表された[19]．それによると，妊娠第一三半期にアシクロビル投与を受けた1561名，バラシクロビル投与を受けた229名の妊娠女性において，やはり児の大きな形態異常の有意な増加は認められなかった．

倫理的な問題からランダム化比較試験が困難な「妊娠とくすり」の分野において，大規模なコホート研究は極めて重要であり，こうした研究の推進がこの分野の進歩には重要である．

妊娠とコルヒチン

痛風発作予防薬であるコルヒチンについては，微小管形成を妨げ有糸細胞分裂を阻害するという作用，およびいくつかのケースシリーズの結果から，従来その妊娠女性への投与による児の異常，特に染色体異常発生への疑念が指摘されていた．これに対して，2010年初めての前向きコホート研究が報告された[20]．それによると，コルヒチン投与を受けた妊娠女性238名（その97%が妊娠第一三半期）において，児の大きな形態異常発生の増加はなく，また染色体異常も認められなかった．ただし，コルヒチン投与群で平均妊娠週数は有意に約1週間短く，早産が約15%と高く，平均出生体重も約300g軽かった．

我が国においては，妊娠可能年齢の女性にコルヒチンを投与することは多くないとは考えられるが，催奇形性の観点からは安全性を示唆する報告として注目される．なお，上記のコルヒチンの作用から，女性のパートナーへの投与に

16) Meador KJ, Baker GA, Browning N et al : Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. New England Journal of Medicine 360 (16) : 1597-1605, 2009
17) Jentink J, Loane MA, Dolk H et al : Valproic acid monotherapy in pregnancy and major congenital malformations. New England Journal of Medicine 362 (23) : 2185-2193, 2010
18) Matok I, Gorodischer R, Koren G et al : The safety of metoclopramide use in the first trimester of pregnancy. New England Journal of Medicine 360 (24) : 2528-2535, 2009
19) Pasternak B, Hviid A : Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. Journal of American Medical Association 304 (8) : 859-866, 2010
20) Diav-Citrin O, Shechtman S, Schwartz V et al : Pregnancy outcome after in utero exposure to colchicine. American Journal of Obstetrics and Gynecology 203 (2) : 144 : e1-e6, 2010

よる児の染色体異常も懸念されているが，これに関する疫学研究報告はない．

妊娠と選択的セロトニン再取り込み阻害薬（SSRI）

SSRIについては，その一種であるパロキセチンの妊娠初期の服用により，児の先天性心疾患のリスクが増加する可能性があるとの2005年のFDAによる警告以来，その後報告された妊娠後期使用による新生児遷延性肺高血圧症の問題を含めて，議論が続いている．

その中で最近注目されるデータは2つある．一つはデンマークから発表されたセルトラリンに関するコホート研究のデータである[21]．それによると，母体が妊娠初期にセルトラリン投与を受けた児259例中4例に心房または心室中隔欠損が認められたという〔オッズ比＝3.25（95%信頼区間：1.21～8.75)〕．このデータはセルトラリンの催奇形性に関する初めての有意な報告であり，今後のさらなる研究が求められる．なお，本報告においては，これまで特に注目されてきたパロキセチンについては有意な催奇形性を認めていない．もう一つはカナダのMotherisk Programからの報告である[22]．妊娠第一三半期に抗うつ薬の投与を受け，生児を分娩した928例についての前向きコホート研究であり，児の大きな形態異常発生のリスク増加は認められなかったという．また，個々の抗うつ薬に関する解析でも特定の形態異常との関係は無かった．

SSRI，さらにそれを含む抗うつ薬と妊娠の問題は，未だ解決されていない．これからも多くの研究成果が報告されると考えられ，臨床医はそれらのデータに注意を払い続ける必要があるだろう．

21) Pedersen LH, Henriksen TB, Vestergaard M et al : Selective serotonin reuptake inhibitors in pregnancy and congenital malformations : population based cohort study. British Medical Journal 339 (7723) : b3569, 2009

22) Einarson A, Choi J, Einarson TR et al : Incidence of major malformations in infants following antidepressant exposure in pregnancy : results of a large prospective cohort study. Canadian Journal of Psychiatry 54 (4) : 242-246, 2009

特集 妊娠と薬物療法

各国が定める妊娠期におけるリスクカテゴリー

吉川　裕之
YOSHIKAWA Hiroyuki

スウェーデンに始まり，米国，豪州など多く国で，リスクカテゴリー分類が作成され，用いられてきた。わが国では，医薬品添付文書に多くの問題点があるが，改訂が進まない状況である。最近，米国のFDA分類の利用が広まりつつあるが，FDA分類においてはA，B，C，D，Xなどのカテゴリーを使わず，記述式になることが決められている。わが国でも個々の薬剤の新リスク分類の確立を目指し，リスク分類の方法論が提唱されるようになった。

Key word　医薬品添付文書，リスクカテゴリー，妊娠期，FDA分類，ADEC分類

はじめに

妊娠中の薬剤の投与は，胎児への有害作用と母体疾患への有用性の両者を勘案し，正しい情報に基づき行われる必要がある。妊娠女性，授乳女性に使用する医薬品が胎児・新生児/乳児に及ぼすリスクを，1978年のスウェーデンに始まり，1979年に米国，1987年にオランダ，1989年に豪州，1991年にデンマークなどがリスクカテゴリーを作成した[1),2)]。母体への有用性も勘案してカテゴリーが決められている。本稿では，わが国の医薬品添付文書，米国食品医薬品局（Food and Drug Administration；FDA）のFDA分類，豪州薬物評価委員会（Australian Drug Evaluation Committee；ADEC）分類を比較し，問題点を指摘したい。妊娠時期（第1，2，3三半期）や授乳期に分けて，リスクが示されていない場合も多い。また，われわれが厚生労働省研究班で検討しているSEA-U分類についても紹介したい。米国においても，FDA分類の改訂作業が進みつつあるので，その方向性を紹介する。なお，これまでの分類は薬剤投与前の判断に役立つように作成されており，妊娠と気づかずに服用するなどの，いわば偶発的服用に対する事後の対応について直接は示していない。

わが国の医薬品添付文書について——FDA分類などとの比較

医薬品添付文書は，唯一薬事法に法的根拠をもつ，最も重要な医薬品に関する情報資料である。現在はインターネットで最新のものを入手可能である。妊娠女性と授乳女性に対する記載は，「使用上の注意」のなかの「妊婦・授乳婦等への投与」の項にある。1997年4月25日に厚生省（現 厚生労働省）から「医療用医薬品添付文書の記載要領について」の通知がなされ，1999年12月末日までに変更がなされたものである。

他の分類と比較するために，「使用上の注意」の表現からあえてFDA分類のようにA，B，C，D，Xと分類することもできる（ただし，FDA分類などの分類上の定義とはまったく異なる）。A：「使用上の注意」の記載が

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ないもの，B：「大量または長期の使用を避けること」，「慎重に使用する」など，C：「有益性投与」，D：「投与を避けることが望ましい」など，X：「投与しないこと」などとなる。そのように分けた場合，FDA分類，ADEC分類にも含まれる403剤について比較すると，X（禁忌）はFDA分類が4.5%，ADEC分類が1.5%に対し，わが国の添付文書では25.3%も存在する[1]。わが国での禁忌に関する大きな問題点を以下に指摘する。

臓器移植後の妊娠では，アザチオプリン，シクロスポリン，タクロリムス水和物などの免疫抑制薬の投与が必須で，それなしでは妊娠継続が不可能だが，わが国では禁忌なのである。つまり，必須の薬剤が禁忌という問題である。

高血圧に対する降圧薬も，カプトプリル，レニベースなどのアンジオテンシン変換酵素阻害薬（ACE-I），ニューロタン，バルサルタンなどのアンジオテンシン受容体拮抗薬（ARB）は羊水過少や胎児死亡を起こすので明らかに禁忌の薬剤である（ただし，FDA分類では第1三半期がC，第2，3三半期がDに分類されており，Xとはなっていない）が，ニフェジピン（カルシウム拮抗薬）やラベタロール塩酸塩（β遮断薬）のように海外では妊娠女性によく使われるものと区別なく「禁忌」となっている。「禁忌」が多すぎて，その根拠に信用がないために，本当に禁忌の薬剤が誤って使われることにつながっている可能性がある。ニフェジピンとラベタロール塩酸塩については，日本産科婦人科学会の要望で検討され，ニフェジピンは妊娠後半期（20週以降）の禁忌が解除され，ラベタロール塩酸塩については妊娠期全体の禁忌が解除され，有益性となることが決定されている。

妊娠時に投与しないことが理由で禁忌となっている薬剤がある。GnRHアゴニスト，経口避妊薬，風疹ワクチンなどであるが，胎児へのリスクが高いという指摘はない。つまり，その使用中に偶然妊娠したとしても中絶の理由にはならない。しかし，「禁忌」となっていることを理由に，実際のリスクは極めて低いにもかかわらず，中絶されることがある。つまり，FDA分類を含め，投与前の評価をしているのであり，投与後の評価とは明確に区別する必要がある。

逆にわが国のほうが投与について規制が緩い薬剤もある[3]。ベンゾジアゼンピン系の薬剤は，わが国では17薬剤中16剤が有益性投与で，ブロチゾラム（レンドルミン）のみが「投与しないことが望ましい」となっている。一方，FDA分類では7薬剤中，X（禁忌）が1剤〔トリアゾラム（ハルシオン）〕，Dが4剤〔ジアゼパム（セルシン），アルプラゾラム（ソラナックス），ロラゼパム（ワイパックス），クロナゼパム（ランドセン）〕，Cが1剤〔ゾルピデム酒石酸塩（マイスリー）〕である（わが国ではこの7剤はすべて有益性投与）。

公的な胎児危険度分類はわが国に存在しないため，実地診療では米国のFDA分類や，豪州のADEC分類などを参考にしていることが多い。つまり，添付文書における文言の微妙な差異は胎児に対する危険度を含意する内容になっているが，統一的なリスクの階層化がなされていない。

現FDA分類と米国添付文書の表記について

1979年，米国のFDAは，医薬品の胎児に対するリスク分類を導入した（表1）[4]。これは，スウェーデンでその1年前に導入されたものを基礎にしている。FDA分類により，添付文書の基本表記が決まっている[5]。

(1) Pregnancy Category A（妊娠カテゴリーA）

添付文書には以下のように表記される。

「妊娠カテゴリーA：妊娠女性における研究で，妊娠の第1（第2，第3，あるいは全）三半期（trimester）に（薬剤名）を投与しても胎児異常のリスクを高めることは実証されていない。この薬剤を妊娠中に使用した場合には，胎児に危害を与える可能性は低いように思われる。しかし，この研究では，危害が生じる可能性を完全には排除できないので，（薬剤名）は，妊娠中には明確に必要な場合にのみ使用するようにしなければならない。」

動物生殖試験のデータもあり，胎児へのリスクを示すことができなかった場合には，添付文書には以下のような表記も加えなければならない。

「生殖試験が（動物名）に，ヒトの用量の最高（X）倍までの用量で実施され，（薬剤名）が原因で妊娠への

表1　FDA分類での定義

A：妊娠女性における適切な比較対照試験において，第1三半期間（first trimester）の胎児へのリスクは証明されず，また，その後の妊娠期間でもリスクがあるという証拠もないもの。
B：動物生殖試験では胎仔へのリスクが証明されず，妊娠女性での適切な比較対照試験が実施されていないもの。あるいは，動物生殖試験でリスクが証明されているが，妊娠女性での第1三半期間の比較対照試験が実施されていない，またその後の妊娠期間でもリスクの証拠がないもの。
C：動物生殖試験では胎仔に有害事象があることが示されているが，ヒトでの適切な比較対照試験が実施されていないもので，妊娠女性での薬剤使用による利益が，潜在的リスクにもかかわらず許容できるもの。あるいは，ヒト，動物ともに試験は実施されていないもの。
D：ヒトにおける調査・市場の経験または研究からの有害反応データに基づいて胎児へのリスクの明らかな証拠が存在するが，妊娠女性での薬剤使用による利益が，潜在的リスクにもかかわらず，許容できるもの（たとえば，生命の危機的状況や重篤な疾病に対して，より安全な薬剤がないか他剤が有効でない場合で，その薬剤が必要であるならば）。
E：動物またはヒトでの研究で胎児異常が証明されている場合，あるいはヒトにおける調査・市場の経験または研究からの有害反応データに基づいて胎児へのリスクの明らかな証拠が存在する場合，あるいは両方の場合。この薬剤を妊婦に使用することは，他のどんな利益よりも明らかにリスクのほうが大きいもの（たとえば，より安全な薬剤か他の治療法が用いうる）。

[Feibus KB：FDA's proposed rule for pregnancy and lactation labeling: improving maternal child health through well-informed medicine use. J Med Toxicology, 4（4）：285-288, 2008より引用]

障害や，胎児への危害を示すエビデンスはなかった。」

(2) Pregnancy Category B（妊娠カテゴリーB）

添付文書には，以下のaまたはbのように表記される。

「a. 生殖試験が（動物名）に，ヒトの用量の最高（X）倍までの用量で実施され，（薬剤名）が原因で妊娠への障害や，胎児への危害を示すエビデンスはなかった。しかし，妊娠女性での適切かつ良好にコントロールされた研究はない。動物生殖試験は必ずしもヒトでの反応を予測できるものではないので，この薬剤は，妊娠中には明確に必要な場合にのみ使用するようにしなければならない。」

「b.（動物名）の生殖試験で，ヒトの用量の（X）倍の用量で（知見を記述）が認められた。しかし，妊娠女性での研究では（薬剤名）が，妊娠の第1（第2，第3，あるいは全）三半期に（薬剤名）を投与しても異常のリスクを高めることは実証されていない。動物実験による知見はあるが，薬剤を妊娠中に用いても，胎児に危害を及ぼす可能性は低いように思われる。しかし，ヒトでの研究で，危害を及ぼす可能性を排除できないので，（薬剤名）は，妊娠中には明確に必要な場合にのみ使用するようにしなければならない。」

(3) Pregnancy Category C（妊娠カテゴリーC）

添付文書には，以下のaまたはbのように表記される。

「a.（薬剤名）は（動物名）にヒトの用量の（X）倍で投与すると，催奇性（あるいは，殺胎児作用その他の有害作用）があることが示されている。妊娠女性での適切かつ良好にコントロールされた研究はない。（薬剤名）は，期待されるベネフィットが胎児への予想されるリスクを検討したうえで正当化されるものである場合にのみ使用するようにする。」

「b. 妊娠カテゴリーC：（薬剤名）に関して動物生殖試験は実施されていない。また，（薬剤名）を妊娠女性に投与して胎児に危害を及ぼす可能性があるかどうか，あるいは生殖能に影響を及ぼす可能性があるかどうかについてもわかっていない。（薬剤名）は，明確な必要性がある場合にのみ妊娠女性に投与するようにしなければならない。」

(4) Pregnancy Category D（妊娠カテゴリーD）

添付文書には，以下のように表記される。

「（薬剤名）は，妊娠女性に投与すると，胎児に危害を及ぼす可能性がある（ヒトのデータ，ならびに関連する動物データがあれば，それも記載）。この薬剤を妊娠中に使用するか，この薬剤を使用中に患者が妊娠した場合には，患者には，胎児への危険性があることを通知しなければならない。」

表2　ADEC分類での定義

A	多数の妊婦および妊娠可能年齢の女性に使用されてきた薬だが，それによって奇形の頻度や胎児に対する直接・間接の有害作用の頻度が増大するといういかなる証拠も観察されていない。
C	催奇形性はないが，その薬理効果によって，胎児や新生児に有害作用を引き起こし，または有害作用を引き起こすことが疑われる薬。これらの効果は可逆的なこともある。詳細は付記した本文を参照のこと。
B1	妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない。動物を用いた研究では胎仔への障害の発生が増加したという証拠は示されていない。
B2	妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない。動物を用いた研究は不十分または欠如しているが，入手しうるデータでは，胎仔への障害の発生が増加したという証拠は示されていない。
B3	妊婦および妊娠可能年齢の女性への使用経験はまだ限られているが，この薬による奇形やヒト胎児への直接・間接的有害作用の発生頻度増加は観察されていない。動物を用いた研究では胎児への障害の発生が増えるという証拠が得られている。しかし，このことがヒトに関してどのような意義をもつかは不明である。
D	ヒト胎児の奇形や不可逆的な障害の発生頻度を増す，または，増すと疑われる，またはその原因と推測される薬。これらの薬にはまた，有害な薬理作用があるかもしれない。詳細は付記した本文を参照のこと。
X	胎児に永久的な障害を引き起こすリスクの高い薬であり，妊娠中あるいは妊娠の可能性がある場合は使用すべきでない。

(5) Pregnancy Category X（妊娠カテゴリーX）

添付文書には，以下のように表記される。

「(薬剤名）は妊娠女性に投与すると，胎児に危害を生じさせる場合がある（ヒトのデータ，ならびに関連する動物データがあれば，それも記載)。(薬剤名）は，妊娠中の女性あるいは妊娠する可能性のある女性には禁忌である。この薬剤を妊娠中に使用するか，この薬剤の使用中に妊娠した場合には，患者には，胎児への危険性があることを通知しなければならない。」

ADEC分類について

豪州のADEC分類〔豪州医薬品評価委員会（ADEC）から発表されている，妊娠と薬に関する公的リスクカテゴリー。表2〕は，基本的にA，B，C，D，Xの5段階に分類され，そのうちBについては動物のデータを考慮して，B1，B2，B3に細分類されている。この分類はADECの先天異常小委員会によって作られた。FDA分類がヒトの研究データと動物実験データから分類されているのに対し，ADEC分類では臨床上での経験が重視されている点が特徴で，禁忌も少ない傾向がある。

FDA分類の改訂への動きと今後のFDA分類

現在，FDAリスク分類は見直しが行われており，カテゴリー分類のみという従来の形式から文章による記述でリスクなどを表記する新しい形式への変更という方向性が示されている。FDA分類として汎用してきたA，B，C，D，Xの添付文書表現を撤廃し，新たな提案を2008年に行った[4]。

1．現FDA分類の問題点

(1) リスクカテゴリーA，B，C，D，Xの問題点

カテゴリーは過度に単純化されており，生殖ならびに発生毒性のリスクを伝えるのに十分ではない。実際にはカテゴリーの判定がリスク増加だけに基づいていないのに，A，B，C，D，Xと文字の順序が進むにつれてリスクが増加するという誤解を生みやすい。カテゴリーDとXはベネフィットを検討して決められている。

同じカテゴリーに属する薬剤は，同じ程度の発生毒性を生じさせるという誤った印象を与える。リスクの重大

性，発生率，タイプがまったく異なる場合でも，同じカテゴリーに分類されることがある。また，リスクが判明している薬剤と判明していない薬剤が，同じカテゴリーに分類されることもある。特にカテゴリーCには，動物実験で生殖に対する有害作用が実証されている薬剤と，動物実験が実施されていない薬剤の両方を含んでいる。

(2) 詳細な情報の不足

リスクの表記では有害作用の重篤度，発生率，内容についてわかりにくく，リスクデータの性質（動物実験データ，ヒトでの観察結果）や，有用性データの品質（統計的有意差，研究デザイン）の区別をしていないため，現行の添付文書は混乱を招くおそれがある。さらに，現行の添付文書では，薬剤の用量，投与期間，頻度，曝露経路，曝露の妊娠とのタイミングに基づいてリスクに違いがあるかについても記載していない。

(3) 予期せぬ偶然の曝露への対応

妊娠女性ならびに妊娠の可能性のある女性での薬物治療に関する方針決定に関わる多くの問題点や，予期せぬ胎児曝露の判断（適用別の懸念，妊娠状態，曝露の程度，偶然の曝露，慢性曝露，曝露のタイミング）に関して十分に対応していない。妊娠中の薬物曝露についての情報が多様な臨床状況に対応できていない。妊娠女性に処方するかどうかの前向きな検討が大部分であり，偶然の曝露に関して後ろ向きの検討をしていることはほとんどない。しかし，妊娠の約50％は計画していなかったものであるので，妊娠が見つかる前に薬剤に偶然曝露する可能性は高い。

2. 第二世代FDA分類の提案[5)]

第二世代のFDA分類が提案されている。大きな改訂点に関するFDAの結論は，以下のようになった。

- 妊娠中の薬剤使用のリスクを特徴づけたり，伝えたりするうえで，A，B，Cというようなカテゴリーシステムは適切とはいえない。
- 使用可能なヒトおよび動物のデータに基づいて薬剤の潜在的リスクを伝えるのには記述式分類方式がよい。

情報としては，児へのリスクの要約（fetal risk summary），臨床的情報（clinical considerations），データ（data）という3つが主要なものである。

第一のリスク要約では，全身に吸収される薬剤とそうでないものに分け，ヒトのデータと動物のデータでリスクの上昇について記述する。

第二の臨床的情報では，予期しない妊娠での胎児へのリスク，妊婦への処方の決定（処方する理由である疾患が母児へ与えるリスク，妊娠中の薬剤量の調整，妊娠時に特異的または増加する母体への薬剤の有害事象，薬剤の量，時期，投与期間の影響，新生児に起こりうる合併症と対応），分娩時の薬剤の影響について記述する。

第三のデータは，まずヒトのデータを，次に動物のデータを記述する。その場合，以下の3点を記述する。研究デザイン，薬剤の情報（量，期間，時期），同定されている胎児の形態異常とその他の有害事象。ヒトのデータでは，ポジティブおよびネガティブな経験，研究対象数，研究期間。動物データでは，研究対象の動物種，ヒトでの投与量と比較した投与量。

わが国のSEA-U分類

妊産婦・授乳婦に使用される医薬品の臨床および非臨床データから催奇形性のリスクを評価する際の基準を検討するとともに，医薬品の添付文書における記載などの情報提供の指針ともなりうる，より一般的かつ詳細で，さらに臨床的対応の原則的指針にも結びつくような日本版薬剤胎児危険度分類基準の確立に向けて，厚生労働科学研究費研究班はSEA-U分類を提唱した（表3）[6)]。ただし本SEA-U分類は，現段階では個々の薬剤の分類ではなく，その分類のための方法論として提案されている。

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4) Feibus KB：FDA's proposed rule for pregnancy and lactati-

表3　SEA-U分類

a）S分類〔ヒト研究（Study）〕

S1：大規模比較対照研究で催奇形性および胎児毒性のいずれも示されていない。

S2：他の研究で催奇形性および胎児毒性のいずれも示されていない。

S3：大規模比較対照研究または他の研究で，軽度・低頻度な催奇形性もしくは胎児毒性が示されている。

S4：大規模比較対照研究または他の研究で，重度・低頻度または軽度・高頻度の催奇形性もしくは胎児毒性が示されている。

S5：大規模比較対照研究または他の研究で，重度・高頻度の催奇形性もしくは胎児毒性が示されている。

SX：上記の研究がない。

b）E分類〔ヒト臨床経験（Experience）〕

E1：20年以上の臨床経験で催奇形性および胎児毒性がどちらも認められていない（リスクがあるという症例報告や経験などが知られていない）。妊娠女性に対して日常的によく用いられる薬剤では10年以上。

E2：10年以上の臨床経験で催奇形性および胎児毒性がどちらも認められていない。妊娠女性に対して日常的によく用いられる薬剤では5年以上。または，類薬1，2において20年以上の臨床経験で催奇形性および胎児毒性のいずれも認められていない。

E3：臨床経験で催奇形性もしくは胎児毒性があるが，軽度かつ低頻度である。

E4：臨床経験で重度・低頻度または軽度・高頻度#5な催奇形性もしくは胎児毒性が認められている。

E5：臨床経験で重度かつ高頻度な催奇形性もしくは胎児毒性が認められている。

EX：臨床経験が10年未満の場合で，催奇形性および胎児毒性のいずれも認められていない。妊娠女性に対して日常的によく用いられる薬剤では5年未満。

c）A分類〔動物実験（Animal experiment）〕

A1：動物実験において，明らかな催奇形性，胚/胎仔/新生仔致死作用，その他の有害作用（変異/骨化遅延，胎仔/新生仔の体重低下，生後の発生指標変化など）が，いずれも認められない。

A2：動物実験において，明らかな催奇形性および胚/胎仔/新生仔致死作用は認められないものの，その他の有害作用（変異/骨化遅延，胎仔/新生仔の体重低下，生後の発生指標変化など）が認められる。類薬で，A0またはA1の条件を満たす。

A3：動物実験において，明らかな催奇形性もしくは胚/胎仔/新生仔致死作用が認められている。類薬での動物実験もこれに含める。

A4：類薬を含め，適切な動物実験データがない。

d）SEA分類に基づくGrading

Grade 1（G1）：S0 E any A any

Grade 2（G2）：S1/X E0 A any，S1/E1/A any

Grade 3（G3）：S1/2 E2/3 A any，SX E1/2 A any，SX/E2/A0/1，SX EX A0/1

Grade 4（G4）：S3/X E3 A any，SX E2/X A2

Grade 5（G5）：S3/4/X E4 A any，S4 E3 A any

e）U分類〔有益性（Utility）〕

U0：より安全な代替可能な薬（G1-3）や他の治療法がない状況がある。

U1：すべての状況で，より安全な代替可能な薬（G1-3）がある。

U2：不要な薬剤。

f）総合評価

A（G1+U0）：児に安全なエビデンスがある。

B（G2+U0）：児にほぼ安全といえる。

C（G3+U0/1，G2+U1）：児に一定のリスクはあるが，必要な場合は投与できる。

D（G4+U0）：特別の状況に限って，使用できる。

X（G5+U0，G4/5+U1，G1/2/3/4/5+U2）：禁忌であり，使用は許容できない。

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Alveolar capillary dysplasia associated with duodenal atresia: Ultrasonographic findings of enlarged, highly echogenic lungs and gastric dilatation in a third-trimester fetus

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Abstract

We report a case of alveolar capillary dysplasia, wherein duodenal atresia was diagnosed during the third trimester. A 36-year-old mother was referred to our hospital for polyhydramnios at 31 weeks' gestation. Duodenal atresia was suspected from the ultrasonographic findings, which showed gastric dilation. Other findings noted were enlarged, highly echogenic lungs, a spherical heart and an increased lung–thorax transverse area ratio. A male infant was born at 37 weeks' gestation. The findings of serial radiography of the infant's upper gastrointestinal tract were compatible with the diagnosis of duodenal atresia; however, he developed persistent pulmonary hypertension of the newborn eight hours after birth and died at five days of age. The autopsy revealed alveolar capillary dysplasia and duodenal obstruction. We propose that the detection of duodenal atresia should prompt the physician to conduct a thorough ultrasonographic examination to rule out associated anomalies, such as alveolar capillary dysplasia, which can be detected by the presence of highly echogenic lungs.

Key words: alveolar capillary dysplasia, duodenal atresia, persistent pulmonary hypertension of the newborn, prenatal diagnosis, ultrasonography.

Introduction

Alveolar capillary dysplasia (ACD), a rare disorder, affects neonates and causes persistent pulmonary hypertension of the newborn (PPHN).[1,2] Although intravenous prostacyclin treatment combined with nitric oxide (NO) inhalation can prolong patient survival, the mortality rate of ACD is 100%. The associated histopathological findings include dysplasia of the alveolar walls and capillaries, with or without misalignment of the pulmonary vessels.

Alveolar capillary dysplasia is associated with congenital anomalies involving the gastrointestinal, cardiovascular, genitourinary and musculoskeletal systems.[3] With recent developments in sonographic diagnostic techniques, such anomalies are more likely to be diagnosed at the fetal stage. Recently, Usui *et al.* reported three cases of ACD with prenatally-diagnosed duodenal atresia; examination of the ultrasonographic findings, retrospectively in two cases, revealed that the fetuses had enlarged echogenic lungs prenatally.[4]

Here, we report another case of ACD resulting in PPHN, wherein duodenal atresia was diagnosed during the third trimester. On the basis of the information gleaned from this case, we propose that the detection of both enlarged, highly echogenic lungs and

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gastric dilatation on fetal ultrasonographic scans may be indicative of ACD associated with duodenal atresia.

Case Report

The mother was a 36-year-old woman with two other healthy children who were born at term and had no significant risk factors. During her third pregnancy, ultrasonography performed in gestational week 28 revealed polyhydramnios, for which she was referred to our hospital in gestational week 31. Subsequent ultrasonographic examination confirmed polyhydramnios and revealed gastric dilatation in the fetus, indicating duodenal atresia (Fig. 1A). We also noted that the lungs were enlarged and hyperechoic compared to the liver; further, the heart appeared to be spherical and the lung–thorax transverse area ratio was elevated (0.78) (Fig. 1B); however, we could not determine the significance of these findings.

In gestational week 33, amniocentesis was performed for karyotyping and ameliorating polyhydramnios, and 2000 mL of amniotic fluid was drained. The karyotype analysis results were normal. In gestational week 37, the mother vaginally delivered a male infant with a birth weight of 2528 g and an Apgar score of 9, both at one and five minutes.

The findings of serial radiography of the infant's upper gastrointestinal tract were compatible with the diagnosis of duodenal atresia and surgery was scheduled; however, he developed PPHN eight hours after birth. Despite NO inhalation and intravenous prostacyclin treatment, PPHN worsened and the planned surgery was canceled. Since the infant's clinical course and prenatal ultrasonographic findings strongly indicated ACD, we recommended that a lung biopsy be performed for the differential diagnosis; however, his parents were not in favor of this or any form of intensive treatment such as extracorporeal membrane oxygenation (ECMO). The infant died at five days of age. An autopsy revealed an intrinsic obstruction of the duodenum above the papilla of Vater, dilatation of the distal blind end of the duodenum, gallbladder hypoplasia, intestinal malrotation, and subglottic and tracheal stenosis involving the cricoid and thyroid cartilages. Microscopic examination revealed thickening of the alveolar septa with the proliferation of capillaries, independent of the alveolar epithelium. Medial hypertrophy was observed in the pulmonary arteries. Pulmonary veins were present in proximity to some of the arteries. All these findings were consistent with the diagnosis of ACD.

Discussion

The incidence of ACD has rarely been discussed; of the 173 reported cases of ACD treated with ECMO, only five involved neonates.[5] ACD is diagnosed usually by performing a lung biopsy or, occasionally, only during

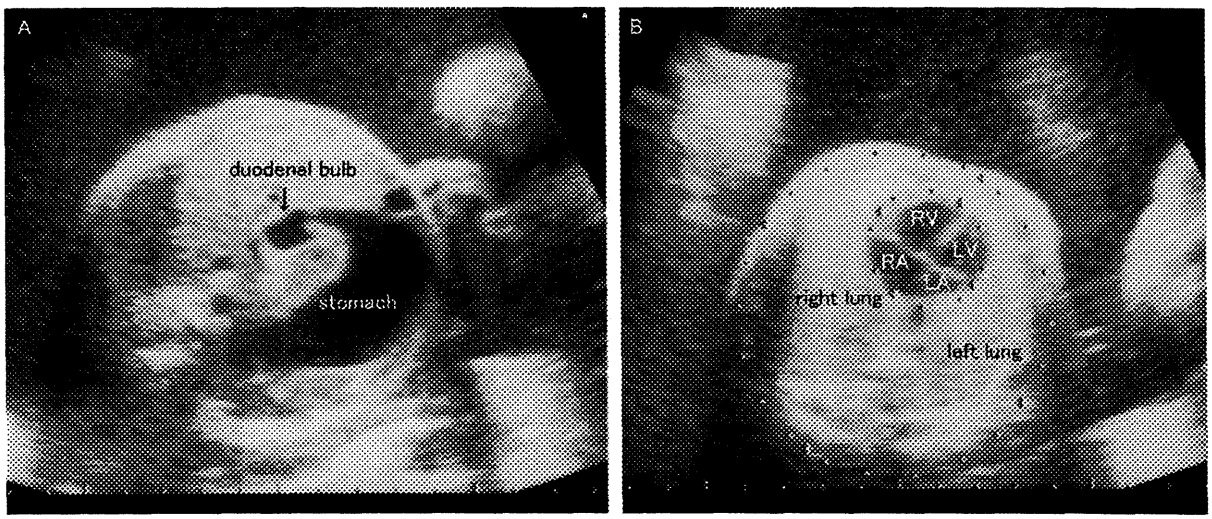

Figure 1 (A) Transverse abdominal ultrasonography image showing gastric dilatation. (B) The four-chamber view shows enlarged, highly echogenic lungs and a spherical heart. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

an autopsy; however, the condition may often be overlooked or misdiagnosed. Moreover, the diagnostic reliability of a lung biopsy is questionable because ACD-associated lesions may be patchy in distribution. Survival is unpredictable with milder forms of the condition.

The pathophysiology of ACD-associated PPHN remains unclear. The following features render ACD distinct from idiopathic PPHN: (i) ACD is not usually governed by predisposing factors such as asphyxia, prematurity and infection; and (ii) there is a latent period – the honeymoon period – from the time of birth to the onset of ACD (mean duration, 48 h).[1] In the present case, the baby was born without asphyxia or infection, and the honeymoon period was eight hours. Further, since the clinical course was typical of ACD, his parents did not provide consent for him to undergo a bronchoscopic biopsy to confirm the diagnosis.

A previous study reported that of the 48 PPHN patients treated, three had ACD and prenatally detected duodenal atresia, accompanied by dilatation of the distal blind end of the duodenum.[4] These findings suggested that a blood-flow disturbance causing duodenal atresia might be relevant to the etiology of ACD, which is characterized by abnormal vasculogenesis. Further, Antao *et al.* reported three cases of ACD associated with gastrointestinal anomalies, one of which had duodenal atresia and anorectal malformation.[6] Gutierrez *et al.*, McGaughran *et al.* and Alameh *et al.* have also reported ACD cases wherein duodenal atresia was diagnosed by prenatal sonography.[7–9]

Usui *et al.* provided the sole available report on the prenatal sonographic findings of ACD.[4] They reported three cases of ACD with pulmonary enlargement and increased echogenicity detected by ultrasonography; these findings implied that each alveolus was enlarged because of fluid retention. In the present case, unusual sonographic findings of enlarged, highly echogenic lungs, a spherical heart and an increased lung–thoracic transverse area ratio were noted. Similar sonographic findings are detected in fetuses with congenital high airway obstruction syndrome (CHAOS).[10] ACD can be differentiated from CHAOS by investigating the patient for the presence of an enlarged fluid-filled trachea with ascites, which is not detectable in the former. CHAOS can be detected by performing a color Doppler study of the dilated airways, which, in the case of CHAOS, shows the absence of flow in the airway throughout the onset of breathing activity.[10] If CHAOS is suspected prenatally, an ex-utero intrapartum treatment procedure may be useful to establish the fetal airway while the fetus is still on placental support. The postmortem finding of subglottic and tracheal stenosis in our patient appear to suggest fluid retention in the lungs.

Fetal gastrointestinal anomalies such as duodenal atresia are easily detected by antenatal ultrasonography. If duodenal atresia is detected prenatally, the physician should undertake a thorough investigation for the detection of other congenital anomalies, even if chromosomal analysis of the fetus shows a normal karyotype. Additionally, ACD should be considered in the differential diagnosis, despite its being a rare condition, and ultrasonographic examination of the fetal lungs should be performed. Findings of gastric dilatation and enlarged, highly echogenic lungs in a third-trimester fetus may indicate ACD associated with duodenal atresia.

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Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2011 edition

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Abstract

Clinical guidelines for obstetrical practice were first published by the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Association of Obstetricians and Gynecologists (JAOG) in 2008, and a revised version was published in 2011. The aims of this publication include the determination of current standard care practices for pregnant women in Japan, the widespread use of standard care practices, the enhancement of safety in obstetrical practice, the reduction in burdens associated with medico-legal and medico-economical problems, and a better understanding between pregnant women and maternity-service providers. These guidelines include a total of 87 Clinical Questions followed by several Answers (CQ&A), a Discussion, a List of References, and some Tables and Figures covering common problems and questions encountered in obstetrical practice. Each answer with a recommendation level of A, B or C has been prepared based principally on 'evidence' or a consensus among Japanese obstetricians in situations where 'evidence' is weak or lacking. Answers with a recommendation level of A or B represent current standard care practices in Japan. All 87 CQ&A are presented herein to promote a better understanding of the current standard care practices for pregnant women in Japan.

Key words: clinical question, complicated pregnancy, guideline, obstetrical practice, recommendation, standard care practice.

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Introduction

In Japan, approximately 1 100 000 women give birth annually at 2800 facilities, at which approximately 8000 obstetricians are employed. Because guidelines for obstetrical practice were not previously available in Japan, remarkable diversity exists among these facilities, particularly with regard to the screening and treatment of fetal/pregnancy abnormalities. This diversity in practice may partly explain the increased number of malpractice lawsuits. The Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Association of Obstetricians and Gynecologists (JAOG) decided to publish guidelines describing standard care practices for pregnant women in 2005. The aims of this guideline are to encourage the widespread use of standard care practices, to enhance the safety of obstetrical practice, to reduce burdens associated with medico-legal and medico-economical problems, and to promote a better understanding between pregnant women and maternity-service providers.

The authors of this article have contributed greatly to the preparation of this draft. The draft was frequently revised as a result of frequent audits and opinions gathered after the publication of the draft in the official Journal of JSOG and on the JSOG and JAOG websites. Then, the first edition, 'Guidelines for Obstetrical Practice in Japan 2008,' consisting of 63 Clinical Questions and 254 Answers (CQ&A), was published in April 2008. The second edition, 'Guidelines for Obstetrical Practice in Japan 2011', containing the revised 63 CQ&A as well as 24 new CQ&A, was published in April 2011.

As these guidelines were originally written in Japanese, non-Japanese speakers have been somewhat inconvenienced; this English version may overcome this problem. The original version of 'Guidelines for Obstetrical Practice in Japan 2011' contains a Discussion, a List of References, and some Tables and Figures. However, these sections have been omitted here because of space limitations.

Implications of 'A', 'B', and 'C' Recommendation Levels

Several tests and/or treatments for pregnant women are presented as answers with a recommendation level of 'A', 'B' or 'C' to each clinical question. The answers and recommendation levels are principally based on evidence or a consensus among Japanese obstetricians when the evidence is considered to be weak or lacking. Thus, the answers are not necessarily based on 'evidence'. The answers usually begin with a verb, which may promote changes in behavior among maternity-service providers in clinical practice. Answers with a recommendation level of A or B are regarded as current standard care practices in Japan. Level A indicates a stronger recommendation than level B. Consequently, informed consent is required when maternity-service providers do not provide care corresponding to an answer with a level of A or B. Answers with a recommendation level of C are possible options that may favorably affect the outcome but for which some uncertainty remains regarding whether the possible benefits outweigh the possible risks. Thus, care corresponding to answers with a recommendation level of C does not necessarily need to be provided. Some answers with a recommendation level of A or B include examinations and treatments that may be difficult for general maternity-service providers to perform. In such cases, the maternity-service providers must refer the patient to an appropriate institution.

Contents

Chapter A. General practice

CQ001: How should uncomplicated healthy pregnant women be cared for prenatally?

Answer

1 Provide antenatal care regularly and try to detect early premature labor, gestational diabetes, pregnancy-induced hypertension, low-lying placenta and placenta previa, fetal abnormalities (fetal growth restriction, abnormal position, oligohydramnios, and polyhydramnios), and placental insufficiency. (A)
2 Measure maternal weight, fundal height of the uterus, and blood pressure; semiquantify glucose

and protein concentrations in the urine; and assess fetal heartbeat and maternal edema at each antenatal visit. (B)
3 Provide antenatal care according to the following schedule: three times until the end of 11 gestational weeks (GW); every 4 weeks between 12 GW and the end of 23 GW; every 2 weeks between 24 GW and the end of 35 GW; and once a week thereafter. (C)
4 Regularly assess the fetal well-being at ≥41 GW. (B)
5 Consider the possibility that midwife-managed care for healthy women, together with existing services (see CQ414), may be clinically effective and may enhance the pregnant woman's satisfaction. (C)

CQ002: What information should be obtained from women during an early stage of pregnancy?
Answer

1 Ask women to complete the questionnaire form (see sample in Discussion). (B)
2 Measure bodyweight and blood pressure and semi-quantify glucose and protein concentrations in the urine. (B)
3 Screen for cancer of the uterine cervix using a cytological examination. (C)

CQ003: What blood tests should be performed during the first trimester?
Answer

1 The following blood tests are recommended: blood typing including ABO and Rh (A), atypical antibody against erythrocyte (indirect Coombs test) (A), complete blood count (A), HBs antigen (A), hepatitis C virus (HCV) antibody (A), rubella antibody using HI (A), screening tests for syphilis (A), human T-cell leukemia virus type 1 (HTLV-1) antibody (A, before the end of the second trimester), screening test for HIV (B), glucose concentration (B), and toxoplasma antibody (C).

CQ004: How should pregnant women with an increased risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) be screened and managed?
Answer

1 Recommend the use of elastic stockings for women with risk factors such as dehydration during emesis, long-term bed rest, obesity, and an older age. (C)
2 Consider the use of unfractionated heparin for women with the highest risk according to the 2004 guidelines for the prophylaxis of DVT/PTE. (C)
3 Do not administer warfarin to pregnant women because of its teratogenicity. As an exception to the rule, warfarin may be considered in pregnant women who have undergone a heart valve replacement. (A)
4 Assess PT, APTT, platelet count, and liver function at appropriate intervals during anti-coagulation with heparin. Measure the platelet count 5–7 days after the initiation of heparin for the early detection of heparin-induced thrombocytopenia (HIT). (B)
5 Try to prevent perinatal DVT/PTE according to the 2004 guidelines for the prophylaxis of DVT/PTE. (B)
6 Rule out DVT prenatally based on symptoms and palpation of both the legs before the postnatal prophylactic use of the intermittent pulse-pressure method. (C)
7 Avoid placing the patient in a 'lithotomy' position when performing a cesarean section. (C)
8 Initiate heparin calcium at a dose of 5000 units twice daily (s.c.) after confirming hemostasis and continue for 3 to 5 days for the prophylaxis of DVT/PTE when anti-coagulation is indicated after a cesarean section. (B)

CQ005: How should patients with hyperglycemic disorders during pregnancy be screened?
Answer

1 Screen all pregnant women for 'gestational diabetes mellitus (GDM)' and 'overt diabetes in pregnancy'. (B)
2 Screen using the following stepwise method: (B)
   1) Measure random blood glucose level at an early stage of pregnancy (each hospital should determine its own cut-off value). Check items ①–③ in Answer 4 before planning a 75-g oral glucose tolerance test (OGTT) in women with a random blood glucose level of ≥200 mg/dL.
   2) Give the pregnant woman a 50-g glucose challenge test (GCT; cut-off value ≥140 mg/dL) or measure the random blood glucose level a second time (cut-off value ≥100 mg/dL) between 24 and 28 GW in women not diagnosed as having 'GDM' or 'overt diabetes in pregnancy'.
3 Give a 75-g OGTT to all women with a positive screening test result except women diagnosed as having 'overt diabetes in pregnancy'. Diagnose the pregnant woman as having 'GDM' if one or more threshold values of a 75-g OGTT are fulfilled. Check items ①–③ in Answer 4 in women with a 2-h plasma glucose (PG) ≥ 200 mg/dL. (A)

Threshold values for 75-g OGTT
① Fasting plasma glucose (FPG) ≥92 mg/dL (5.1 mmol/L)
② 1-h PG ≥ 180 mg/dL (10.0 mmol/L)
③ 2-h PG ≥ 153 mg/dL (8.5 mmol/L)

4 Diagnose the pregnant woman as having 'overt diabetes in pregnancy' if any of the following three criteria are fulfilled. (A)
① FPG ≥ 126 mg/dL
② HbA1c ≥ 6.5%, expressed as National Glycohemoglobin Standardization Program (NGSP) value (HbA1c ≥ 6.1% according to Japan Diabetes Society [JDS])*
③ Definite diabetic retinopathy
④ Random blood glucose ≥200 mg/dL with any of ①–③, or 2-h PG ≥ 200 mg/dL with any of ①–③.

*The HbA1c value (%) according to the NGSP criteria corresponds to the same value plus 0.4 according to the JDS criteria.

5 Give a 75-g OGTT to all women with 'GDM' at 6–12 weeks postpartum. Assess the degree of glucose intolerance once again in all postpartum women diagnosed as having 'overt diabetes in pregnancy'. (C)

CQ006: How should patients with thyroid dysfunction during pregnancy be screened?

Answer

1 Determine the TSH, free T3, and free T4 levels in the blood of women with suspicious clinical signs and/or a medical history of thyroid dysfunction. (B)
2 Try to normalize the thyroid function of patients with thyroid dysfunction. Consult appropriate specialists or other appropriate experts if any difficulty is encountered while treating the patient. (A)

CQ007: How should women visiting a clinic and complaining of decreased fetal movements be dealt with?

Answer

1 Tell the patient, 'Some investigators have suggested that decreased fetal movements are associated with fetal jeopardy.' (C)
2 Assess the fetal well-being in an appropriate manner, such as a non-stress test (NST). (B)

CQ008: How should women with an atypical antibody against red blood cells be treated? (see CQ302 for women with ant-Rh [D] antibody)

Answer

1 Identify the antibody when a screening test, such as the indirect Coombs test, suggests the presence of an atypical antibody against red blood cells. (B)
2 Assess the titer of the antibody if the antibody belongs to an immunoglobulin (Ig) G that may cause hemolysis in the fetus. (B)
3 Monitor the fetal well-being, paying special attention to anemia and hydrops, in women with an elevated titer of an IgG antibody that may cause hemolysis in the fetus. (B)
4 Be prepared to administer un-crossmatched packed red blood cells compatible with an ABO blood type if the pregnant woman develops unexpected massive bleeding. (B)

CQ009: How should the expected date of confinement (EDC) be determined?

Answer

1 Determine the EDC based on the last menstrual period (LMP) in principle, but use the date of ovulation or fertilization if available. (A)
2 Use the EDC based on the crown–rump length (CRL) in cases with a CRL of 14–41 mm if the difference in the EDC is ≥7 days from the EDC based on the LMP. (B)
3 Use the EDC based on the biparietal diameter (BPD) and the femur length (FL) in cases with an estimated 12–19 GW and/or a CRL of >50 mm if the difference in the EDC is ≥10 days from the EDC based on the LMP. (C)
4 Estimate the EDC according to Answer 3, with careful consideration of fetal growth restriction (FGR) and post-term pregnancy, after taking possible deviations into account in cases with an estimated GW of ≥20. (C)
5 Determine the EDC based on findings of the early neonate if no relevant information is available prenatally. (C)

CQ010: What guidance regarding maternal body composition and weight gain during pregnancy should be provided?

Answer

1 Provide the following information when asked about the association between maternal body composition and pregnancy outcome. (C)
1) Lean women (body mass index [BMI] < 18.5 before pregnancy) are at an increased risk for preterm labor, preterm delivery, and low birthweight newborns.

2) Obese women (BMI ≥ 25 before pregnancy) are at an increased risk for pregnancy-induced hypertension, gestational diabetes mellitus, stillbirth, fetal macrosomia, and fetal neural tube defects.

2 Provide the following information when asked about weight gain during pregnancy. (B)
1) Japanese women of normal body composition (18.5 ≤ BMI < 25) are estimated to require a weight gain of 11 kg as of the 40th GW to have a singleton newborn weighing 3 kg, according to the 'Dietary Reference Intakes for Japanese' published by the Ministry of Health, Labour, and Welfare, Japan (2010). However, considerable individual differences exist.
2) Maternal weight gain during pregnancy is correlated with the birthweight of the newborn. However, this correlation becomes weaker as the pre-pregnancy maternal BMI increases. In cases of obese women, the pre-pregnancy BMI, rather than the weight gain during pregnancy, tends to affect the birthweight of the newborns more strongly.

3 Consider the following items when providing nutritional advice.
1) Recommend a balanced intake of nutrients. (A)
2) Use the pre-pregnancy BMI. (B)
3) Note that maternal weight gain is one of the parameters for assessing the maternal nutritional condition, and several different guidelines for maternal weight gain during pregnancy exist in Japan. (B)
4) Moderate nutritional guidance for pregnant women is preferred because high-quality evidence is not available. (C)

Chapter B. Consultation

CQ101: Which vaccines are safe for pregnant and lactating women?

Answer

1 Viable vaccines are contraindicated, in principle, for pregnant women. (A)
2 Non-viable vaccines can be given to pregnant women. (B)
3 Both viable and non-viable vaccines can be given to lactating women. (B)

CQ102: What considerations are necessary regarding the administration of vaccines against influenza and antiviral drugs to pregnant women?

Answer

1 Administer vaccines after explaining that the benefit of vaccination outweighs the risk derived from infection with influenza when women want to be vaccinated. (B)
2 Consider that the benefit outweighs the risk of using antiviral drugs, such as oseltamivir and zanamivir, for the treatment of influenza in pregnant and lactating women. (C)
3 Consider that the benefit outweighs the risk of using antiviral drugs, such as oseltamivir and zanamivir, for the prophylaxis of influenza in pregnant and lactating women after they have come in close contact with an infected person. (C)

CQ103: How should women anxious about the adverse effects of radiation exposure during pregnancy be treated?

Answer

1 Before counseling, determine the dose of the exposure and the stage of pregnancy (GW) when the exposure occurred using the last menstrual period, measurement of the conceptus by ultrasonography, or the date of a positive pregnancy test result. (A)
2 Explain that the risk of a fetal anomaly does not increase in cases with exposure within 10 days after conception. (B)
3 Explain that an embryo at stages ranging from 11 days after conception until 10 GW is vulnerable but does not have an increased risk of malformation at doses of <50 mGy. (B)
4 Explain that the central nervous system of a fetus at 10–27 GW may be affected unfavorably at doses of ≥100 mGy. (B)
5 Explain that a dose of 10 mGy is associated with a subtle, but negligible, increase in the risk of childhood cancer. (B)

CQ104: How should women who ask questions regarding the effects of a drug on the fetus be answered?

Answer

1 First determine the date on which the drug was taken and the corresponding GW. Use the last menstrual period, the date of a positive pregnancy test (urinary human chorionic gonadotrophin [hCG] level), and an ultrasound measurement to estimate the GW accurately. (A)
2 Refer to Table 1, a textbook such as 'Drugs in Pregnancy and Lactation,' by Briggs *et al.* (Lippincott Williams and Wilkins) or information on the

Internet. Inform the woman of the service provided by the Japan National Center for Child Health and Development. (B)

CQ105: How should one respond when asked about the association between folic acid and the occurrence of neural tube defects (NTD) in the fetus?

Answer

1 Explain as follows. (B)
   1) A reduction in the risk of an NTD is expected if 0.4 mg of folic acid is taken as a daily supplement prior to the establishment of pregnancy.
   2) A reduction in the recurrent risk of an NTD is expected when a woman who has previously given birth to an infant with an NTD takes 4.0–5.0 mg of folic acid daily under the supervision of a physician.

CQ106: How should women in whom a thickened nuchal translucency (NT) is incidentally found be treated?

Answer

1 Remember that the accurate measurement of an NT requires the following:
   1) A stage of pregnancy between 10 and 14 GW. (C)
   2) Sufficient magnification of the upper trunk of the fetus. (C)
   3) Measurement on a sagittal section as shown in the figure. (C)
2 Explain the implications of a thickened NT to women who have agreed to be informed of the results of antenatal diagnosis using ultrasonographic testing. (B)
3 Remember that some women do not wish to know the results of antenatal diagnosis. (A)
4 Consider the ethical problems involved in both situations described in Answers 2 and 3. (A)
5 Explain that the implications of a thickened NT are as follows: (C)
   1) A fetus with an NT of ≥3 mm, 4 mm, 5 mm, or 6 mm has a 3-times, 18-times, 28-times, and 36-times higher risk than the risk based on maternal age, respectively, of having 21-trisomy, 18-trisomy, or 13-trisomy, as shown in Figure 2.
   2) More than 90% of fetuses with a normal karyotype but with an NT of ≥3.5 mm survive without developing any congenital diseases.
   3) Approximately 70% of fetuses with a chromosomal aberration have an NT that is ≥95th percentile value and that increases from 2.1 mm to 2.7 mm with advancing gestation during the 11th to 14th GW. The 99th percentile value for NT is 3.5 mm, independently of the GW.
   4) Chromosomal analysis using amniotic fluid is needed for a definite diagnosis of chromosomal aberration.

CQ107: How should one respond when asked about the effects of a drug during lactation on neonates/infants?

Answer

1 Assure the patient that most drugs, with a few exceptions, are not harmful to neonates/infants when taken while a woman is lactating. (B)
2 Recommend that the condition of the child, such as the speed of suckling, sleep status, mood and activity, and weight gain, be observed when a lactating woman decides to take a drug for which some concern over possible unfavorable effects exists. (C)
3 Refer to a textbook such as 'Drugs in Pregnancy and Lactation,' by Briggs *et al.* (Lippincott Williams and Wilkins) or visit the website of the Japan National Center for Child Health and Development. (C)

CQ108: How should one respond to questions regarding exercise during pregnancy?

Answer

1 Exercises to develop adequate strength may contribute to the maintenance and promotion of a healthy lifestyle. (B)
2 No evidence exists supporting any favorable effects of exercise on the prevention of pregnancy-induced hypertension, gestational diabetes mellitus, or prolonged labor. (C)
3 Women with the following complications should refrain from regular exercise. (A)
   1) Serious diseases of the heart and lung.
   2) Threatened preterm labor, cervical incompetency, shortened uterine cervix, or premature rupture of the membranes.
   3) Genital bleeding, placenta previa, or a low-lying placenta.
   4) Pregnancy-induced hypertension.
4 Women should refrain from the following exercises. (B)
   1) Exercises requiring a supine or standing position with minimal movement for long periods of time.
   2) Activities with an inherent increased risk of falling or traumatic injuries.
   3) Scuba diving.
5 Women with the following symptoms should discontinue all exercise: dizziness, headache, chest

pain, dyspnea, muscle weakness, calf pain or a swollen calf, uterine contractions or discomfort in the abdomen, decreased number of fetal movements, and bleeding or an increased watery discharge from the vagina. (B)

6 An appropriate heart rate target zone should be maintained while performing aerobic exercise. (B)

CQ109: How should pregnant women who smoke or who are exposed to passive smoking be treated?

Answer

1 Ask women about their smoking status at an early stage in their pregnancy. (B)
2 Recommend that women quit smoking. (B)
3 Respond as follows when asked about the effects of active and passive smoking: (B)
Active and passive smoking have unfavorable effects on human health, pregnancy outcomes, and fetal and child development and health.
4 Recommend that the woman's partner quit smoking. (C)
5 Recommend that women avoid passive smoke. (C)

Chapter C. Obstetrical complications during the first trimester of pregnancy

CQ201: How should women with hyperemesis gravidarum be treated?

Answer

1 Recommend 'frequent small meals' and the frequent intake of salt-containing fluids, such as sports drinks. (A)
2 Administer i.v. fluids in patients with dehydration. (A)
3 Add thiamine hydrochloride (vitamin B1) to the fluid to prevent Wernicke's encephalopathy. (A)
4 Consider the administration of oral pyridoxine (vitamin B6). (C)
5 Be cautious of the possible occurrence of deep vein thrombosis. (C)

CQ202: How should women with a presumed abortion at <12 GW be treated?

Answer

1 Consider the possibility of an ectopic pregnancy. (A)
2 Diagnose as a 'missed abortion' after at least two examinations performed at an appropriate time interval. (B)
3 Treat patients with abortions as follows.
1) For patients with missed, incomplete, or progressive abortions, active treatment with surgical evacuation is recommended, although conservative treatment without surgical procedures may be feasible. Provide information regarding the risks of unscheduled procedures to any remaining conceptus *in utero* even after surgical evacuation, and be cautious of possible molar or ectopic pregnancies. (B)
2) For patients with complete abortions, only follow up without surgical intervention is sufficient. (C)

CQ203: How should patients with ectopic pregnancy be treated?

Answer

1 An ectopic pregnancy should be suspected in women with a positive pregnancy test result (urinary or serum hCG) who exhibit any of the following signs. (B)
1) No gestational sac (GS) within the uterus.
2) A GS-like mass outside the uterus.
3) A considerable amount of fluid in the Douglas pouch.
4) Signs indicative of a reduction in the circulating blood volume (anemia, tachycardia, or hypotension).
5) No chorionic villi in the evacuated conceptus.
6) Complaints suggestive of an acute abdomen.
2 Choose surgical, medical, or expectant management after a careful assessment of the general condition of the patient, the site of the ectopic pregnancy, the hCG value, the presence or absence of fetal cardiac activity, and the volume of the abnormal mass in the pelvic cavity. (B)
3 Closely monitor patients who are being treated medically or expectantly with caution for intra-abdominal bleeding, persisting ectopic pregnancy, and chorionic diseases. (B)
4 Confirm a non-pregnant level of hCG during a follow-up examination of patients treated medically or expectantly. (C)
5 Remember that the incidence rate of heterotopic pregnancy is higher among women using assisted reproductive technology than among women with natural conception. (C)

CQ204: How should women with recurrent pregnancy loss be treated?

Answer

1 Diagnose patients with ≥3 successive spontaneous abortions as having 'habitual abortion'. (A)
2 Try to reduce the anxiety of couples through supportive counseling. (B)

3 Provide the following information: (C)
Sixty to seventy percent of couples with unexplained habitual abortions will go on to have successful pregnancies without any specific treatment, although the success rate of the next pregnancy varies according to maternal age and the number of previous abortions. Investigations of the causes of habitual abortions are able to disclose a specific cause in only 50% of couples with habitual abortions.
4 Recommend the following examinations if the couples want to seek the cause of the habitual abortions.
1) Anti-phospholipid antibodies, including lupus anticoagulant, anticardiolipin antibody, and anti-cardiolipin β2GP1 antibody. (A)
2) Quantity of coagulation factors. (C)
3) Chromosomal analysis of the patient and the partner after obtaining informed consent. (B)
4) Transvaginal ultrasonography, hysterosalpingography, and/or hysteroscopy for the detection of anatomical deformities of the genital tract. (A)
5) Endocrinological environment. (C)
5 Diagnose patients with habitual abortion as having 'antiphospholipid antibody syndrome' if they test positive for an anti-phospholipid antibody ≥2 times. (A)
6 Remember that 'paternal lymphocyte immunization' is only effective in women with certain characteristics. Conduct lymphocyte immunotherapy using irradiated lymphocytes only after a serious consideration of the indications (see corresponding paragraph in the Discussion). (A)

CQ205: What cautions are required for induced abortion (dilatation and curettage) at <12 GW?
Answer

1 Before the procedure, confirm the last menstrual period, parity, and the presence or absence of asthma, drug allergies, and current use of drugs. (A)
2 Before the procedure, confirm the anatomical features inside and outside of the uterus using digital and ultrasonographic examinations. (A)
3 Perform the following preoperative examinations: blood typing including ABO and Rh (D) (B), a complete blood count (B), electrocardiography before or during the procedure (C), and tests for the detection of infections such as hepatitis B virus (HBV). (C).
4 Obtain informed consent as to possible complications arising from the anesthesia or procedure. (C)
5 Confirm that oxygen is easily available. (A)
6 Confirm the presence or absence of chorionic villi in the evacuated conceptus. (A)
7 Confirm the completeness of the procedure using *trans*-vaginal ultrasonography just after the procedure. (C)
8 Perform a second *trans*-vaginal ultrasonography examination 1 week after the procedure. (C)

CQ206: How should women with genital bleeding with or without abdominal pains (threatened abortion) at <12 GW be treated?
Answer

1 For patients with undetectable fetal cardiac activity during an ultrasonography examination, consider the possibility of early-stage pregnancy, missed abortion, ectopic pregnancy, trophoblastic disease, and incomplete or complete abortions as differential diagnoses. (B)
2 Remember that no drugs have been proven to be effective for improving pregnancy outcomes. (B)
3 In patients with detectable subchorionic hematoma and fetal cardiac activity, consider bed rest as a possible treatment. (C)

Chapter D. Obstetrical complications during the second and third trimesters of pregnancy

CQ301: How should women with suspected cervical incompetence be treated?
Answer

1 Treat women suspected of having cervical incompetency based on their history of previous pregnancies using either of the following modalities: (B)
1) Follow up the current pregnancy conservatively with special attention to the length and dilatation of the uterine cervix.
2) Use prophylactic cervical cerclage.
2 Treat women suspected of having cervical incompetency based on the course of the current pregnancy using either of the following modalities: (A)
1) Monitor patients closely using cautions similar to those for patients with threatened abortion/preterm labor.
2) Use therapeutic cervical cerclage.
3 Use prophylactic cervical cerclage soon after ≥12 GW. (B)
4 Control any infection first if the patient shows clinical signs of an infection, such as fever, leukocytosis, and/or an elevated serum C-reactive protein level. (C)

CQ302: How should pregnant women with a blood type of negative Rh (D) be treated?

Answer

1 Treat women without anti-Rh (D) antibody as follows:
   1) Administer anti-D immunoglobulin within 72 h after the delivery of an Rh (D)-positive infant. (A)
   2) Assess the anti-Rh (D) antibody titer at least twice around 28 weeks and peripartum. (B)
   3) Administer anti-D immunoglobulin to women around 28 weeks for the prevention of Rh(D) alloimmunization, after obtaining informed consent. (B)
   4) Administer anti-D immunoglobulin to women with the following characteristics to prevent Rh(D) alloimmunization. (B)
      - Termination of pregnancy with a viable embryo at ≥7 weeks, including miscarriage, induced abortion, and ectopic pregnancy.
      - After invasive procedures, such as amniocentesis and external cephalic version of breech.
      - A traumatic hit to the abdomen.
2 In women with anti-Rh (D) antibody, measure the anti-Rh (D) antibody titer every 2 weeks during the latter half of pregnancy. (B)
3 In patients who show a significant increase in the anti-Rh (D) antibody titer, assess fetal well-being with respect to anemia and hydrops fetalis. (A)

CQ303: How should women with preterm labor be treated?

Answer

1 Remember that women with the following characteristics have a high risk for preterm delivery. (A)
   Current pregnancy: multiple pregnancy, bacterial vaginosis, and/or shortened uterine cervix.
   History: previous preterm delivery and/or postconization of the uterine cervix.
2 Diagnose as preterm labor in cases with regular uterine contractions and/or premature maturation of the uterine cervix (dilatation of the cervix and/or shortened cervical length) and recommend that these patients be admitted to the hospital and/or given a tocolytic drug. (B)
3 Suspect a placental abruption in patients with an abnormal fetal heart rate (FHR) pattern. (B)
4 Measure the maternal body temperature, white blood cell count, and C-reactive protein (CRP) level and initiate antibiotic therapy if an intrauterine infection is suspected. (C)
5 Consider an early delivery in patients suspected of having an amniotic fluid infection. (C)
6 Cooperate with hospitals having neonatal intensive care unit (NICU) beds, if necessary. (B)
7 Administer betamethasone (12 mg twice, i.m., at an interval of 24 h) to women if delivery at 22–33 GW is considered to be inevitable. (B)

CQ304: How should women with premature rupture of the membranes (PROM) be treated?

Answer

1 Refrain from frequent digital examinations and examine the vagina and uterine cervix using Cusco's speculum to minimize the risk of ascending infection. (B)
2 Assess the body temperature, pulse rate, tenderness of the abdomen, complete blood count (CBC), CRP level, and NST findings (at ≥26 weeks) at an adequate interval to detect 'clinical chorioamnionitis' and to confirm fetal well-being. (C)
3 Consider an early delivery within 24 h in a patient diagnosed as having 'clinical chorioamnionitis' at ≥26 GW. (C)
4 Monitor the FHR patterns continuously in parturient febrile (≥38.0°C) women at ≥26 GW and pay attention to maternal septicemia. (B)
5 Induce labor or expect the onset of spontaneous labor in cases with ≥37 GW. (B)
6 Treat women with 34–36 GW in a similar way to women with ≥37 GW. (C)
7 Treat women with <34 GW as follows:
   1) Refer the patient to a facility with NICU beds or cooperate with a facility with NICU beds in treating the patient. (B)
   2) Treat expectantly with the administration of antibiotics, in principle. However, an early delivery is also an acceptable option in some situations. (C)
8 Administer steroids to a mother with <32 GW to facilitate fetal lung maturation and to prevent fetal intracranial hemorrhage (see CQ303). (B)
9 Treat women with <26 GW according to the policy of each hospital. (B)

CQ305: How should women with placenta previa be treated?

Answer

1 Screen all women around 20 GW with ultrasonography for the detection of women with an increased risk of placenta previa and diagnose as placenta