■ 妊娠中の薬剤の安全性に関する相談は妊娠と薬情報センターで行っている.

■ 授乳中の薬剤使用に関する情報は同センターのホームページで閲覧できる.

後述する妊娠と薬情報センターのホームページには授乳可能な薬剤と，授乳を避けるべき薬剤をリストにして掲載しているので参考にしていただきたい.

相談機関

妊娠中の薬剤使用に関する主な相談機関は下記の通りである.

・国立成育医療センター「妊娠と薬情報センター」(http://www.ncchd.go.jp/kusuri/index.html)

妊娠中の薬剤使用に関する情報提供ならびに症例のデータベース構築を目的に2005年10月に厚生労働省の事業として発足した[4].

・虎の門病院「妊娠と薬相談外来」

・聖路加国際病院「妊娠と薬相談クリニック」

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特集　小児疾患と妊娠・周産期・トランジション

Ⅱ．小児科医が知っておくべき妊娠中の注意事項

妊産婦と薬剤

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要旨　妊娠・授乳中の薬物使用は慎重であるべきであることはいうまでもないが，治療上，必要な薬は使用せざるを得ない場合もある．よって，われわれはその薬物が妊娠・授乳に与える影響をきちんと理解し評価したうえで患者側に説明し，使用することが重要になってくる．本稿では安全性の評価の考えかた，日常診療での使用頻度の高い薬の安全性について，それらの情報の収集方法についてまとめる．

Key words　薬，安全性，妊娠，授乳

はじめに

「妊娠中の薬の使用はできるだけ避けたい」と考える一般女性はまだ多いが，その一方で妊婦の高齢化に伴う合併症妊娠のために薬剤を使用しなければならないケースも増えてきている．また，慢性疾患を抱えた女性が妊娠を考えた際には，妊娠前から薬で原疾患がしっかりコントロールされていることにより妊娠転帰がよくなるという事実もある．よって，薬が妊娠に与える影響については，正しい情報に基づき患者側へ説明したうえで処方する必要がある．本稿では妊娠中の薬物治療の考えかたについて述べたい．

薬の安全性の評価

1．総　論

妊娠中に薬剤を使用していた妊婦に流産や児の先天異常があった場合，まず薬剤の影響が疑われがちである．しかし，薬剤を内服していなくても，全分娩のうち約3%においては先天異常（奇形）が発生し，自然流産の発生率は15%前後であることを患者も医師も知っておく必要がある．そして，奇形全体のうち薬剤が原因とされている奇形は，抗てんかん薬のようなリスクが明らかでも内服を継続せざるを得ないケースを含めてもわずかに1%以下である．

妊娠中の薬剤の影響を考える際には，まず曝露を受けた時期が重要になってくる．妊娠時期は胎児発生の観点から図[1]に示すように，着床前期（受精から約2週間の時期：妊娠3週まで），胎芽期（妊娠4～9週），胎児期（妊娠10週以降）に分けられる．着床前期においてはall or none（全か無か）の時期であり，この時期に問題となる薬を使用していたとしても，有害な影響を受けた卵は着床しないか流産となるため，児に奇形をきたすことはないとされている．胎芽期は器官形成期であり，とくに4～7週にかけてはもっとも重要な時期となる[1]．この時期に問題となる薬剤を投与すると催奇形性をきたすおそれがある（表1）．ただし，催奇形性の時期は臓器によって異なってお

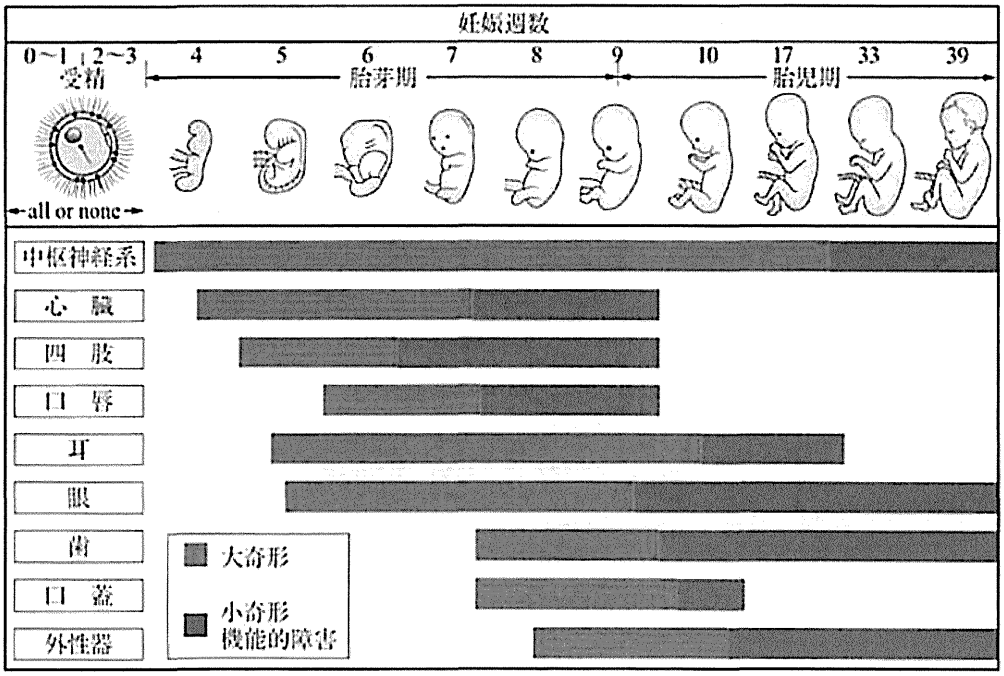

図　胎児の発生における危険期（文献1）より引用）

表1　催奇形性のあるおもな薬剤

薬　剤	異常の内容
サリドマイド	アザラシ肢症
男性ホルモン	女性外性器の男性化
クマリン誘導体（ワルファリンなど）	鼻の低形成
ビタミンA誘導体	耳小症
D-ペニシラミン	弛緩性皮膚
抗てんかん薬	神経管欠損症など
メトトレキサート	頭蓋骨早期癒合による顔貌異常，四肢異常
ミソプロストール	Möbius症候群，四肢切断
チアマゾール	頭皮欠損など
炭酸リチウム	Ebstein奇形
ミコフェノール酸モフェチル（MMF，セルセプト®）	顔面異常
ステロイド	口唇口蓋裂

表2　胎児毒性のあるおもな薬剤

薬剤の種類	症　候
非ステロイド抗炎症薬（NSAIDs）	動脈管早期閉鎖による肺高血圧症，羊水減少，分娩遷延
アンジオテンシン変換酵素（ACE）阻害薬/アンジオテンシンⅡ受容体拮抗薬（ARB）	胎児の低血圧と腎血流低下による頭蓋冠低形成や腎機能異常
抗甲状腺薬	甲状腺機能低下，甲状腺腫
過剰なヨード	甲状腺機能低下
抗精神病薬	新生児薬物離脱症候群
アルコール	胎児性アルコール症候群
喫　煙	胎児発育遅延

NSAIDs:non-steroidal anti-inflammatory drugs, ACE:angiotensin converting enzyme, ARB:angiotensin Ⅱ receptor blocker

り，たとえば口蓋などは10週までとなっている．10週以降は胎児期になり，この時期の薬剤投与は胎児毒性が問題となる（表2）．また，中枢神経系についてはその後も大事な時期が続く．

2．添付文書と医師の裁量権

わが国の添付文書では「妊婦または妊娠している可能性のある婦人には投与しないこと」（妊婦禁忌）となっている薬剤が多いが，中には禁忌とした根拠が合理的でない薬剤が含まれている．禁忌薬となっていても，これまでの臨床データの蓄積からおそらく使用しても問題ないと考えられている薬がある一方，絶対的に禁忌薬とすべきものもある．基本的な姿勢としては，妊娠している女性への薬剤投与も添付文書に沿って行われるべきではあるが，現実として医師の裁量権で判断し，使用せざるを得ない場面もあり，われわれは薬剤投

与に際してどのように安全性を評価すべきか理解しておく必要がある．そのことを念頭に，以下に薬剤の安全性の評価に関する考えかたをまとめる．

薬剤が市場に流通するまでには治験にて，安全性，有効性が確認されているが，妊婦を対象にした治験は倫理上，不可能であるため，発売された段階で妊娠中の影響に関するデータは動物実験結果のみである．しかし実際は，ヒトに対する催奇形性物質の動物における偽陰性は3%，ヒトに対する非催奇形性物質の動物における偽陽性は72%であり（表3）[3]，奇形発生の動物とヒトとの一致率には大きな開きがある．動物実験結果がそのままヒトに適応できるわけではないことを理解しておく必要がある[3]．したがって，添付文書に「妊婦または妊娠している可能性のある婦人には，治療上の有益性が危険性を上回ると判断される場合にのみ投与すること」（有益性投与）とあっても，発売直後の薬剤の妊娠中の使用は控えるのが無難である．一方で動物実験を根拠にいつまでも妊婦禁忌となっている薬剤が存在することも知っておく必要がある．ドンペリドンは妊婦禁忌となっている制吐薬であり，悪阻と知らずに悪心を主訴に受診した妊婦に処方されている例が多いことは容易に想像できるが，これまでに催奇形性を疑うような報告はなされていない．

3．臨床での対応

妊娠可能年齢の女性に問題となる薬を処方する際には，計画妊娠の指導が重要となる．最近は一般販売されている妊娠確認検査薬の精度も向上しており，医療機関で使用されている検査薬とほとんど変らない精度で妊娠反応の確認が可能となっている．したがって，日頃より妊娠初期の内服が問題となる薬を処方する際には，そのリスクを説明するとともに，仮に妊娠が判明した際にはただちに受診してもらい，薬剤変更をする旨を説明しておくことが重要である．また，通に予期しない妊娠をした場合であるが，その薬剤が影響するリスクについての客観的な情報を提供し，安易な中絶をすることのないようにするとともに，あわせてベースラインリスクが3%程度はあること説明しておくことが必要となる．必要に応じて「妊娠と薬情報センター」[4]のような施設でのカウンセリングを受けてもらうのも一つの方法である．

表3　ヒトと動物の催奇形性成績の一致率
文献3）より引用

動物種	ヒトの催奇形性因子（38）陽性反応	ヒトの非催奇形性因子（165）非陽性反応
マウス	85%	35%
ラット	80%	50%
ウサギ	60%	70%
ハムスター	45%	35%
サル	30%	80%
2種類以上の動物種	80%	51%
すべての動物種	21%	28%
いずれかの動物種	97%	79%

また，妊娠可能年齢の女性に薬剤を処方する際には，意図しない妊娠がおこる可能性を考えて，問題となる薬を安易に処方しないことも念頭においておく必要がある．

日常診療で使用する頻度の高い薬剤の安全性

1．解熱鎮痛薬・片頭痛治療薬

妊娠中に第1選択で使用される解熱・鎮痛薬はアセトアミノフェンである．非ステロイド抗炎症薬（non-steroidal anti-inflammatory drugs，以下NSAIDsと略す）全体としては催奇形性の報告はされていないが，長期連用や妊娠後期（29週以降）の使用により，産前産後の出血，胎児動脈管の収縮作用，羊水量の減少や新生児遷延性肺高血圧（persistent pulmonary hypertension of the newborn，以下PPHNと略す）などが報告されており，禁忌となっている．また，添付文書上は妊娠全期間を通して禁忌となっている薬もあるので注意が必要である．

片頭痛の治療に対してもまず，アセトアミノ

フェンが第1選択になる．緊張型頭痛の因子を含む軽度の片頭痛にはNSAIDsも有効である．トリプタン製剤は歴史が浅く，スマトリプタン（イミグラン®）以外は妊婦に対する使用についてのデータはほとんどなく，安全性が確立しているとはいえない．片頭痛の予防目的にプロプラノロール（インデラル®）を使用する場合には，長期の使用による胎児発育遅延などの報告があることに留意しながら使う必要がある．

2．消化器系薬剤

H_2受容体拮抗薬やプロトンポンプ阻害薬（proton pump inhibitor:PPI）は妊娠期間中に使用する場面がしばしばあるが，疫学研究でリスクは否定されている．とくに注意を要する薬剤としてはプロスタグランジン製剤のミソプロストール（サイトテック®）があり，流産や奇形の原因となるので，妊婦のみならず妊娠可能女性には投与しない．制吐剤のメトクロプラミド（プリンペラン®），ドンペリドン（ナウゼリン®）はいずれもヒトでの催奇形性の報告はないが，ドンペリドンは動物実験での催奇形性を理由に禁忌となっているため制吐薬を使用する際にはメトクロプラミドを使用する．なお，授乳に関しては相対的乳児投与量（relative infant dose，以下RIDと略す）が，メトクロプラミド4.4%，ドンペリドン0.04%であり，ドンペリドンのほうが児への移行は少ない．

3．抗菌薬

妊娠期・授乳期に使用する抗菌薬の第1選択薬としてはセフェム系，ペニシリン系，マクロライド系があげられる．ニューキノロン系は，添付文書上は禁忌となっているが，疫学研究のリスクは否定的である．

4．抗アレルギー薬（抗ヒスタミン薬）

第1世代抗ヒスタミン薬に関しては一般的に奇形が発生に対する影響はほぼないことが科学的に証明されている．しかし，ヒドロキシジン（アタラックス-P®）は995例対象のメタアナリシスでリスクが棄却されているにもかかわらず，口蓋裂，離脱症状の症例報告があり，米国でも禁忌であることから，2006年6月にわが国でも禁忌となっている．

第2世代の抗ヒスタミン薬においては，セチリジン（ジルテック®），ロラタジン（クラリチン®）は妊娠中の使用に関する疫学調査において，リスクが低いことが示されている．しかし，ロイコトリエン受容体拮抗薬，メディエーター遊離抑制薬，トロンボキサンA_2合成阻害薬，Th2サイトカイン阻害薬のほとんどがわが国で開発されたもので，疫学研究はほとんどない．

5．向精神薬

抗うつ薬が流産，早産，胎児発育遅延のリスクと関連しているとの報告があるが，うつ状態自体が早産や胎児発育遅延のリスク増加に関連するとの報告もある．よって，これらのリスクを理由に薬剤の使用を控える必要はない．選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor:SSRI）については妊娠期間の後半に使用するとPPHNの発症率が増加するとの報告や，パロキセチン（パキシル®）で心奇形のリスクが上がるという報告もあるが，これを否定する報告もあり結論は出ていない．バルプロ酸（デパケン®，セレニカR®）は催奇形性があることがわかっているため，双極性障害で内服している場合には非定型抗精神病薬への変更を考慮する．リチウムはEbstein奇形の発生率が最大で1/20,000→1/1,000に上昇するリスクはあるが，現実に薬剤変更できない際には，臨床的に大きな問題となるリスクの上昇ではないことを説明のうえで使用する．

向精神薬が母体から経胎盤的に胎児へ移行していた影響により，新生児薬物離脱症候群となるおそれがある．症状は1週間以内におこることが多く，分娩施設の医師に使用薬剤について情報提供をしておく必要がある．また，「スリーピングベビー」として生れてくる可能性があるため，新生児蘇生が可能な施設での分娩が望ましい．

妊娠中に向精神薬が必要と予想される場合に

は，妊娠前から薬剤を整理し，薬剤の変更や減量，中止したうえでも病状が安定していることを確認しておく．自己判断での治療中断や減量による原疾患の悪化によって，かえって妊娠への悪影響があることを認識させておく必要がある．

向精神薬使用が長期的にみて児の発達に影響するかどうかについては，出生後のさまざまな環境因子も影響するため十分な研究を行うことができていないのが現状である[5]．

6．漢方薬

漢方薬は欧米でほとんど使用されていないため，妊娠中の使用に関する疫学研究の報告がなく，妊娠や胎児に与える影響について十分な評価を行うことができていないことを念頭におくべきである．大黄，牡丹皮，附子，桃仁，牛膝，硫酸ナトリウム・無水芒硝は添付文書上，「妊婦または妊娠している可能性のある婦人には投与しないことが望ましい」（禁忌希望）となっている．

7．ビタミン剤

過剰摂取に注意が必要なのはビタミンAである．高用量のビタミンAではレチノイド胎児病を招くので，妊娠中は5,000 IU/日以上の摂取は避けるべきだといわれている．なお，妊娠を計画しているすべての女性に対して神経管閉鎖障害の発症リスクを低減させるために葉酸400 μg/日の摂取が推奨されている．

8．アルコールと喫煙

アルコールが胎児に及ぼす影響として，流産，死産，先天異常の他，胎児アルコール症候群（fetal alcohol syndrome：FAS）（特異的な顔貌，出生前後の発育不全，精神遅滞や多動症などの中枢神経系の異常）や胎児アルコール効果（fetal alcohol effect：FAE）（中枢神経障害が主体）が明らかになっており，妊婦の飲酒は避けるべきである．

喫煙（ニコチン）は妊孕性の低下，流・早産，低出生体重児の増加の他，児の発がん，呼吸器感染症，気管支喘息，中耳炎のリスク因子となる．さらに乳児突然死症候群（sudden infant death syndrome：SIDS），発育不全，精神発達の遅れ，注意欠陥多動性障害（attention deficit hyperactivity disorder：ADHD）が指摘されている．とくに受動喫煙でもリスクが高いので注意が必要である．

表4　添付文書に男性使用時の避妊について記載があるおもな薬剤（重複含む）

避妊となる理由	薬剤名
薬剤の精液中への移行	サリドマイド，レナリドミド，リバビリン
遺伝毒性の可能性	コルヒチン，リバビリン，ガンシクロビル，アザチオプリン，バルガンシクロビル
精子形成能の異常	エトレチナート，タミバロテン，ミグルスタット

※未分類：メトトレキサート，レフルノミド
（各製薬会社の添付文書，インタビューフォームをもとに作成）

男性の薬剤使用と胎児への影響

表4は添付文書上，男性使用時の避妊について記載があるおもな薬剤である．添付文書で避妊を指示する理由は大きく三つあげられる．①薬剤の精液中への移行，②遺伝毒性の可能性，③精子形成能の異常，である．まず①については，通常は射精後の精液は腟内にとどまり，子宮頸管粘液を超えて子宮内に侵入できるのは精子のみであること，精液への薬剤移行はきわめて少なく，腟壁からの吸収もわずかであることから，まず影響はないと考えてよい．②については減数分裂後の精子細胞ではDNA修復能は停止するので，精子細胞のDNAに損傷がおこった後でも受精能を有する精子になることができれば，理論的には胎児死亡や次世代に引き継がれる異常をひきおこす可能性がある．③については，妊孕性の低下が問題となる．

授乳中に注意すべき薬剤・物質

母親が服用した薬が母乳栄養の児に作用するためには，①母乳への移行，②児の消化管からの吸収，という2段階を経なければならない．しか

表5　妊娠・授乳と薬などに関する情報源

情報源	特　徴
Drugs in Pregnancy & Lactation	この分野の成書といえる．現在では2011年の第9版が最新版である
Chemically Induced Birth Defects	薬剤だけでなく，化学物質や食品が胎児に及ぼす影響についての情報がある．動物実験の情報が詳しく記載されていることがある
Maternal-Fetal Toxicology:A Clinician's Guide	妊娠中の母体の変化やそれによる薬剤の体内動態，胎児毒性，新生児薬物離脱症候群の解説，職業曝露の影響，母乳中への薬剤移行の考えかたなど広く内容を理解するのに役立つ
Medication and Mothers' Milk	授乳と薬に特化した教科書
薬物治療コンサルテーション 妊娠と授乳	妊娠と薬情報センターを中心として集められた情報がまとまっている書籍
LactMed	米国National Library of Medicineの中のTEHIPが運営しているTOXNETとよばれるデータベースの一つにあたる．オンライン上で無料で閲覧可能．現在もっとも参考となる情報源 http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
REPROTOX	オンライン上で利用可能な有料サイト．授乳や精子や男性機能への影響についても記載 http://www.reprotox.org/
TERIS	オンライン上で利用可能な有料サイト．催奇形性や胎児毒性についての情報のみで授乳に関する情報は含まれていない http://depts.washington.edu/terisweb/teris/
妊娠と薬情報センターホームページ	授乳に関する薬剤について公表されている http://www.ncchd.go.jp/kusuri/index.html

TEHIP:Toxicology and Environmental Health Information Program，REPROTOX:Reproductive Toxicology Center System，TERIS:Teratogen Information System

し，わが国の医薬品添付文書には，母乳へわずかでも移行すれば授乳を中止するように記載されており，母乳栄養児の血液中にほとんど検出されない薬までもが授乳禁忌になっており，母乳のメリットを考慮すると安易に母乳を中止すべきでない．

問題になる因子としては，①一定量以上，母乳に分泌され，乳児に影響を与える，②蓄積性がある，③毒性が強い，④児の未熟性（新生児早期，早産児），⑤（腸からの）吸収率および生物学的利用率，があげられる．乳汁中の薬剤移行についてはM/P比（milk/plasma）とRIDを考慮する．

$$RID = \frac{\text{母乳を介する薬の用量（mg/kg/日）}}{\text{乳児の治療量（mg/kg/日）}} \times 100\%$$

※乳児の治療量の決まっていない時は，母親の体重あたりの治療量でも代用できる．

注意すべき薬剤としては，フェノバルビタール，エトスクシミド，プリミドン，テオフィリン，リチウム，ヨード製剤などがある．具体的なリストは「妊娠と薬情報センター」のホームページ[4]に掲載されている．また，アルコールについては，乳児に影響のない飲酒の安全量は確立されておらず，授乳中は禁酒が必要である．

情報の入手方法

前述のとおり，日本の医薬品添付文書から得られる情報のみで診療を行うことは，エビデンスに基づいた治療を行っているとはいえず，われわれは過去のデータの蓄積から得られた情報に基づき診療を行っていくべきである．参考になる情報源を表5にまとめたので，参考にしていただきたい．ここに示した情報源は二次情報であるため，オンラインであっても最新の情報に更新されていない可能性があり，合せて一次情報検索を行う必

要もある．

なお，安全性の判断資料として，これまで米国食品医薬品局（Food and Drug Administration：FDA）のA－B－C－D－X分類（いわゆるFDA分類）が参考にされてきたが，A－B－C－D－Xの順にリスクの大きさを表しているとの誤解が広く生じている点や，妊娠に気づかずに曝露された胎児への情報が欠けているなどの理由から，2008年より用いられていない．現在，カテゴリー形式から記述式への変更作業が進行中である[8]．また，米国小児科学会（American Academy of Pediatrics：AAP）による授乳に関する声明[6]も2010年8月に失効し，改訂の予定はない[7]．

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OBSTETRICS

Outcomes of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009

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OBJECTIVE: To assess adverse fetal outcomes and short-term prognoses of infants exposed to oseltamivir or zanamivir in utero during pandemic (H1N1) 2009 in Japan.

STUDY DESIGN: Case series study. We asked the 2611 obstetric facilities in Japan that are members of the Japan Society of Obstetrics and Gynecology to participate, and data were provided from 157 facilities. We evaluated the numbers of pregnancy complications and neonatal abnormalities.

RESULTS: We evaluated 624 infants born to 619 women given oseltamivir and 50 infants born to 50 women given zanamivir. Of patients given oseltamivir before gestational week 22, 3 experienced miscarriage and 1 experienced induced abortion. The overall rate of congenital malformations was 2.1% (14/670). In infants exposed during the first trimester, the rate of malformations was 1.3% (2/156) with oseltamivir and 0.0% (0/15) with zanamivir, although in infants exposed during the second and third trimesters, this rate was 2.6% (12/464) with oseltamivir and 0.0% (0/35) with zanamivir. Increased rates of miscarriage in women given antiviral drugs before gestational week 22 (0.9% [3/322]), preterm delivery in women given antiviral drugs before gestational week 37 (5.5% [33/600]), stillbirth (0% [0/670]), neonatal death (0.15% [1/670]), birthweight <2500 g (8.7% [58/670]), small-for-gestational-age infants (8.4% [56/670]), necrotizing enterocolitis (0.0%), intraventricular hemorrhage (0.0%), seizures (0.15% [1/670]), and other transient abnormalities in the neonatal period (4.3% [29/670]) were not observed in those exposed to antiviral drugs before the corresponding episodes or complications.

CONCLUSION: Short-term prognoses of infants exposed to oseltamivir or zanamivir in utero were not adversely affected.

Key words: antiviral drugs, case series study, fetal outcome, pregnancy complication

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As high morbidity and mortality rates of pregnant women were expected in the beginning of pandemic (H1N1) 2009,[1] the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommended the use of neuraminidase inhibitors such as oseltamivir or zanamivir in pregnant patients thought to be infected with the novel virus.[2,3] The Japan Society of Obstetrics and Gynecology (JSOG) also recommended the use of oseltamivir or zanamivir for the treatment of pregnant patients or for prophylaxis in pregnant women in close contact with an infected person.[4-6] It has been reported that early antiviral drug use and admission to an intensive care unit decreases the risk of maternal death because of pneumonia.[7-9]

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Vaccination against pandemic (H1N1) 2009 influenza during pregnancy had the benefits of reducing the risk of stillbirth[10] and not increasing the risk of adverse fetal outcome.[11] At that time, the safety of oseltamivir use in pregnancy was based on findings from 137 women who took oseltamivir during pregnancy,[12] although 2 papers were published later.[14,15] Pregnancy outcomes were available for only 9 women exposed to zanamivir during pregnancy.[12] These data suggested oseltamivir is unlikely to cause adverse pregnancy or fetal outcomes, but the available data were limited. The safety of zanamivir in pregnancy was still unknown. Therefore, JSOG conducted this prospective study in collaboration with Chugai Pharmaceutical Co, Ltd, (Tokyo, Japan) to collect more information on pregnant women and fetuses exposed to antiviral drugs such as oseltamivir and zanamivir.

Materials and Methods

This prospective study was conducted after approval by the institutional review

board at the University of Toyama (Toyama City, Japan). In August 2009, we asked all 2611 obstetric facilities in Japan that are members of JSOG to participate, and data were provided from 157 facilities. Pregnant women who visited physicians at these facilities to discuss prophylaxis or treatment of influenza were fully informed of the purpose of this study. When these women were given oseltamivir or zanamivir and consented to participate in this study during the 15-month period between Oct. 1, 2009, and Dec. 31, 2010, their obstetricians prospectively registered them at the Current Medical Information Center (CMIC) Co Ltd (Tokyo, Japan) registration center using an electronic data capture system or postal mail. A total 725 pregnant women were registered from 157 facilities and followed up. The registration center (CMIC Co Ltd) successively collected the following maternal and neonatal clinical data through the physicians who registered individual cases: maternal demographic characteristics such as maternal age; gestational week when contracting influenza and taking oseltamivir or zanamivir; vaccination against the novel H1N1 influenza and/or seasonal influenza; and pregnancy outcomes including gestational week at delivery, birthweight of infant, stillbirth, or live birth, neonatal death within 60 days after birth, congenital malformations, periventricular leukomalacia, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, seizures, and other transient abnormalities such as febrile condition, hyperbilirubinemia (total bilirubin level; term infant ≥17 mg/dL, preterm infant ≥15 mg/dL), transient tachypnea of newborn, and hypoglycemia (blood sugar level; term infant <40 mg/dL, preterm infant <30 mg/dL). Intracranial hemorrhage and periventricular leukomalacia were diagnosed by ultrasonography and/or magnetic resonance imaging. Small for gestational age was defined as a birthweight below the 10th percentile for gestational age of Japanese infants.[16] Congenital cardiac abnormalities in neonates were confirmed by neonatologists or cardiologists using echocardiography. The follow-up periods of these infants were 1 to18 months.

Of 725 registered women, 56 were excluded from this analysis on the basis of indeterminate neonatal information (n = 6), postpartum drug therapy (n = 5), administration of both oseltamivir and zanamivir (n = 1), administration of laninamivir (n = 2), administration of other treatment (n = 18), administration of unknown drugs (n = 4), unknown time of drug administration and maternal infection (n = 16), and administration of drugs at less than 4 weeks' gestation (n = 4) (Figure). An influenza detection kit was used to diagnose 333 cases, and 84 cases were diagnosed by clinical symptoms.

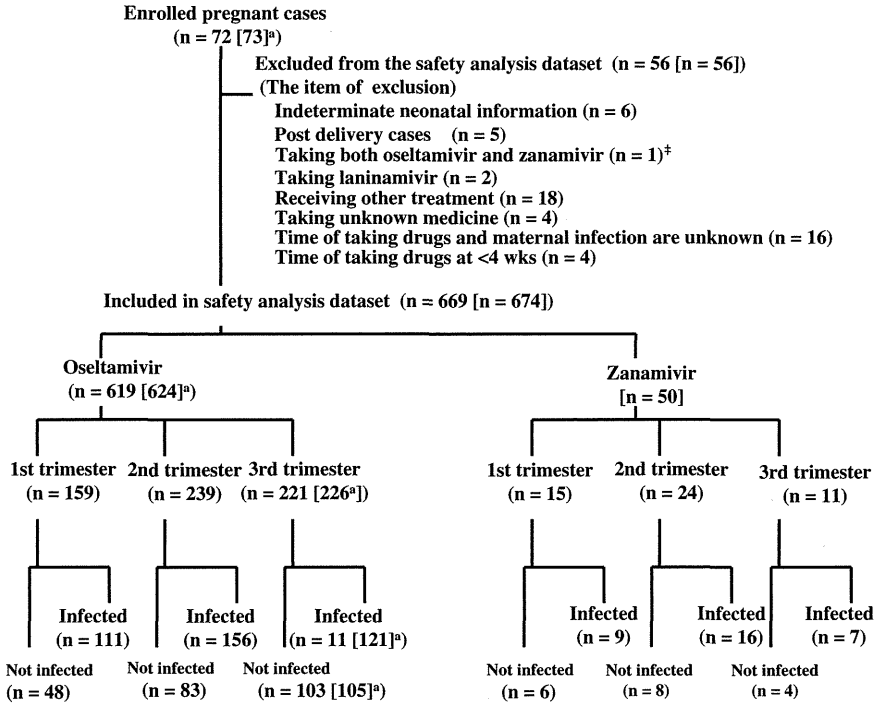
Statistical analysis

The χ^2 test was used to compare patient baseline characteristics among the oseltamivir and zanamivir groups and the infected and noninfected groups. The unpaired Student *t* test was used to compare days from onset to treatment between oseltamivir and zanamivir. A *P* value of < .05 was considered statistically significant.

RESULTS

A total 619 women took oseltamivir alone, with 624 fetuses (including 5 sets of twins) exposed to oseltamivir, and 50 women took zanamivir alone, with 50 fetuses exposed to zanamivir; 417 women, with 420 fetuses (including 3 sets of twins), contracted influenza. Of the 669 women, 37.7% (252) took antiviral drugs for prophylaxis after close contact with an infected person (Figure and Table 1). We first studied whether influenza infection itself affects the maternal and fetal outcomes. Other risk factors for miscarriage, malformed infants, low-birthweight infants, and small-for-gestational-age infants, such as maternal age 35 and over, smoking, and alcohol use, were similar between infected and noninfected groups. In the infected group, 70% of patients developed a fever of 38°C or higher,

FIGURE
Six hundred fifty infants born to 646 women analyzed in this study



[a]Neonates; [‡]One woman who took both oseltamivir and zanamivir was assigned to both oseltamivir and zanamivir groups, and thus the total number of women is 647. Four women with twin pregnancies took oseltamivir. The number of infants is shown in parentheses.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

TABLE 1
Characteristics of pregnant women given antiinfluenza drugs according to influenza infection status

Variable	Infected	Noninfected	*P* value
Number of women	417	252	
Age ≥35 y	95 (22.8) 18.8–27.1	87 (34.5) 28.7–40.7	.0009
Multiple pregnancy	3 (0.7) 0.1–2.1	2 (0.8) 0.1–2.8	.9140
Smoking, yes	19 (4.6) 2.8–7.0	9 (3.6) 1.6–6.7	.5376
Alcohol use, yes	10 (2.4) 1.2–4.4	4 (1.6) 0.4–4.0	.4778
Vaccination (during pregnancy), yes	115 (27.6) 23.3–32.1	124 (49.2) 42.9–55.6	< .0001
Fever (≥38°C), yes	292 (70.0) 65.4–74.4	1 (0.4) 0.0–2.2	< .0001
Timing of administration			
1st trimester	120 (28.8) 24.5–33.4	54 (21.4) 16.5–27.0	0358
2nd trimester	172 (41.2) 36.5–46.1	91 (36.1) 30.2–42.4	.1876
3rd trimester	125 (30.0) 25.6–34.6	107 (42.5) 36.3–48.8	.0010
Days from onset to treatment, mean ± SD (min, 25%, 50%, 75%, max)	0.37 ± 0.81 day (0,0,0,1,9)		

Data shown as the number (%) 95% confidence interval.

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although the frequency in the noninfected group was only 0.4%. The frequency of vaccination during pregnancy in the noninfected group was significantly higher than that in the infected group (49.2% vs 27.6%, $P < .0001$). There were no significant differences in frequencies of miscarriage, stillbirth, neonatal death, preterm delivery, low-birthweight infants, small-for-gestational-age infants, infants with congenital malformations, and other abnormalities in infants such as infection, hyperbilirubinemia, hypoglycemia, transient tachypnea, respiratory distress syndrome, pyrexia, hypothyroidism, necrotizing enterocolitis, intraventricular hemorrhage, convulsion, vomiting, periventricular leukomalacia, and hypernephroma between the infected and noninfected groups, suggesting that influenza infection did not induce miscarriage, stillbirth, neonatal death, preterm delivery, low-birthweight infants, small-for-gestational-age infants, or malformed infants in this study (Table 2).

Characteristics of pregnant women in oseltamivir and zanamivir groups are shown in Table 3. Baseline characteristics in both groups were similar.

The rates of neither miscarriage nor preterm deliveries appeared to be increased in either group (Table 4). Only 3 (1.0%) of 294 women who took oseltamivir before gestational week 22 experienced miscarriage. There were no miscarriages in 27 women who took zanamivir before gestational week 22. These frequencies were lower than those

TABLE 2
Pregnancy outcomes with exposure to antiinfluenza drugs according to influenza infection status

Variable	Infected	Noninfected	*P* value
Number of outcomes	420	254	
Miscarriage at <22 wks	3 (1.3) 0.3–3.9	0	.2521
Induced abortion	1 (0.2) 0.0–1.3	0	.4364
Stillbirth	0	0	—
Neonatal death	1 (0.2) 0.0–1.3	0	.4342
Preterm delivery			
<37 wks	20 (5.2) 3.2–8.0	13 (5.9) 3.2–9.9	.7069
<28 wks	1 (0.3) 0.0–1.9	0	.4775
Low birthweight <2500 g	34 (8.2) 5.7–11.2	24 (9.4) 6.1–13.7	.5689
Small for gestational age	29 (7.0) 4.7–9.9	27 (10.6) 7.1–15.1	.0969
Infants with congenital anomalies	8 (1.9) 0.8–3.8	6 (2.4) 0.9–5.1	.6998
Congenital heart defect	7 (1.7) 0.7–3.4	4 (1.6) 0.4–4.0	.9151
Deformity (excluding congenital heart defect)	2 (0.5) 0.1–1.7	2 (0.8) 0.1–2.8	.6172
Minor skeletal change	0	1 (0.4) 0.0–2.2	.2003
Other adverse birth outcomes	23 (5.5) 3.5–8.2	6 (2.4) 0.9–5.1	.0507

Data shown as number (%) 95% confidence interval.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

TABLE 3
Characteristics of pregnant women given antiinfluenza drugs according to drug type

Variable	Oseltamivir	Zanamivir	*P* value
Number of women	619	50	
Age ≥35 y	167 (27.0) 23.5–30.7	15 (30.0) 17.9–44.6	.6443
Maternal infection infected	385[a] (62.2) 58.2–66.0	32 (64.0)[b] 49.2–77.1	.8002
Multiple pregnancy	5 (0.8) 0.3–1.9	0	.5235
Smoking, yes	26 (4.2) 2.8–6.1	2 (4.0) 0.5–13.7	.9458
Alcohol use, yes	12 (1.9) 1.0–3.4	2 (4.0) 0.5–13.7	.3273
Vaccination (during pregnancy), yes	223 (36.0) 32.2–39.9	16 (32.0) 19.5–46.7	.5677
Treated	363 (58.6) 54.6–62.6	30 (60.0) 45.2–73.6	.8513
Fever (≥38°C), yes	272 (43.9) 40.0–48.0	21 (42.0) 28.2–56.8	.7901
Timing of administration			
1st trimester	159 (25.7) 22.3–29.3	15 (30.0) 17.9–44.6	.5036
2nd trimester	239 (38.6) 34.8–42.6	24 (48.0) 33.7–62.6	.1910
3rd trimester	221 (35.7) 31.9–39.6	11 (22.0) 11.5–36.0	.0502
Days from onset to treatment mean ± SD (min, 25%, 50%, 75%, max)	0.36 ± 0.81 day (0,0,0,1,9)	0.39 ± 0.79 day (0,0,0,0,3)	.8181

[a] Infected patients comprised 304 patients diagnosed with a rapid test (type A, 298; type B, 3; and type A and B, 3) and 81 patients diagnosed with clinical symptoms; [b] Infected patients comprised 26 patients diagnosed with a rapid test (type A, 25 and type B, 1) and 6 patients diagnosed with clinical symptoms.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

reported by Nybo Andersen[17] (13.5%) and in the report from the Ministry of Health and Welfare study of 827 Japanese cases from 1991 to 1993 (14.9%).[18] Twenty-nine (5.2%; 95% confidence interval [CI], 3.5–7.4%) of 553 pregnant women who took oseltamivir and 4 (8.5%) of 47 pregnant women who took zanamivir before gestational week 36 experienced preterm delivery (Table 4). The frequency of preterm delivery with oseltamivir was similar to that in Japanese national data from 2009 (5.70% [60.989/1,070,035]; 95% CI, 5.66–5.74%).[19] The frequency with zanamivir was slightly higher than that in the 2009 Japanese national data; however, the 95% CI (2.4–20.4%) of preterm delivery in zanamivir did not exceed that in the national data (Table 4).

The rates of neither convulsion nor other transient abnormalities such as transient tachypnea, respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, infection with fever, hypothyroidism, and vomiting appeared to be increased compared with those that have been reported (Table 5).[13] In Japan, prevalence of infants with a birthweight <2500 g was 9.6% in 2009[19] and that of small-for-gestational-age infants was 10% in 1998.[16] Therefore, the rates of birth weight <2500 g and small-for-gestational-age infants exposed to oseltamivir or zanamivir did not exceed those in Japanese national data (Table 5). No infants developed necrotizing enterocolitis or intraventricular hemorrhage (Table 5). Suspected periventricular leukomalacia was found on magnetic resonance imaging in one infant with a birthweight of 1794 g born at 31 weeks to a woman who contracted influenza at 15 weeks (Table 6). However, periodic follow-up until 1 year of age revealed consistently normal neurologic development. Periventricular leukomalacia accounts for more than 50% of cerebral palsy cases among premature infants.[20] The prevalence of moderately severe or severe cerebral palsy was approximately 2 per 1000 live births in 1994, and infants with birthweight <2500 g account for approximately a third of all infants with cerebral palsy.[21] Thus, the case of suspected periventricular leukomalacia may have resulted from prematurity. One infant exhibited seizures and proved to have agenesis of corpus callosum (Table 6, case 26). One small-for-gestational-age infant with a birthweight of 776 g was stillborn at 28 weeks to a mother who contracted influenza at 8 weeks and developed placental abruption, which occurs in approximately 1 in 100 Japanese women.[22] Another infant with a birthweight of 662 g was born at 24 weeks to a mother in the zanamivir treatment group who developed influenza 1 day before labor onset; the infant died 36 days after birth because of prematurity.

A total of 14 infants (2.1%, 14/670) were confirmed to have congenital malformations within 1 to 18 months after birth (Table 5). The overall rates of malformations were 2.3% (14/620) for infants exposed to oseltamivir alone and 0% (0/50) for infants exposed to zanamivir alone. The rate of congenital malformation in infants exposed to oseltamivir or zanamivir during the period of organogenesis is very important. Of the 14 infants, only 2 were

exposed to an antiviral drug (oseltamivir) during the first trimester (Table 3). In infants exposed during the first trimester, the rate of malformations was 1.3% (2/156) with oseltamivir and 0.0% (0/15) with zanamivir, although in infants exposed during the second and third trimesters, this rate was 2.6% (12/464) with oseltamivir and 0.0% (0/35) with zanamivir. There were no cases of congenital heart defects or other deformities in infants exposed to oseltamivir or zanamivir during gestational weeks 4 to 7. In infants exposed during gestational weeks 8 to 14, the frequencies of congenital heart defects and other deformities were both 0.9% (1/113) with oseltamivir although there were no such defects or deformities with zanamivir. Thus, antiviral drugs taken during the very sensitive first trimester did not increase the risk of malformation. Details on congenital malformations are shown in Table 5.

Eight of the 14 infants with congenital malformations were born to mothers who contracted influenza during pregnancy (Table 2). Therefore, the rate of congenital malformations did not appear to be associated with maternal influenza infection (1.9% [8/416] for infected women vs 2.4% [6/254] for noninfected women).

TABLE 4
Pregnancy outcomes with exposure to antiinfluenza drugs according to drug type

Variable	Oseltamivir	Zanamivir	*P* value
Number of outcomes	624	50	
Miscarriage at <22 wks	3 (1.0) 0.2–3.0	0	.5979
Induced abortion	1 (0.2) 0.0–0.9	0	.7770
Stillbirth	0	0	—
Neonatal death	0	1 (2.0) 0.1–10.6	.0004
Preterm delivery			
<37 wks	29 (5.2) 3.5–7.4	4 (8.5) 2.4–20.4	.3457
<28 wks	0	1 (2.6) 0.1–13.5	.0015
Low birthweight <2500 g	53 (8.5) 6.5–11.0	5 (10.0) 3.3–21.8	.7255
Small for gestational age	54 (8.7) 6.6–11.2	2 (4.0) 0.5–13.7	.2471
Infants with congenital anomalies	14 (2.3) 1.2–3.8	0	.2829
Congenital heart defect	11 (1.8) 0.9–3.2	0	.3423
Deformity (excluding congenital heart defect)	4 (0.6) 0.2–1.6	0	.5689
Minor skeletal change	1 (0.2) 0.0–0.9	0	.7763
Other adverse birth outcomes	24 (3.9) 2.5–5.7	5 (10.0) 3.3–21.8	.0405

Data shown as number (%) 95% confidence interval.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

COMMENTS

This prospective study suggests that the use of oseltamivir and zanamivir does not increase the number of adverse pregnancy outcomes, including congenital malformation.

Comparison with other studies

This prospective case series study is substantially larger than previous studies. Because the available studies dealt with only a limited number of women who took oseltamivir during pregnancy at the beginning of pandemic (H1N1) 2009,[12] JSOG collected more clinical data on oseltamivir use during pregnancy in Japan. A paper available on June 5, 2009, reported that 3 (2.2%) of 137 women exposed to oseltamivir at an unknown point during pregnancy (although at least 42 of them took oseltamivir between gestational week 4 and 7) had 3 infants with major congenital abnormalities comprising 1 case each of trisomy 21, anencephaly, and ventricular septal defect.[12] More recent studies showed the rates of major malformations in infants exposed to antiviral drugs to be 0% (0/137),[8] 4.7% (4/86),[14] and 9.0% (9/100).[15] Donner et al[15] reported the safety of oseltamivir in pregnancy using the Roche oseltamivir safety database; however, our data were not included in that report. In our study, the rate of major malformations was 2.3% (14/620) in the oseltamivir-exposed group, and this rate was 1.3% (2/156) in fetuses exposed to oseltamivir during the first trimester. When our data were added to the earlier reports, the malformation rate was 2.8% (30/1053) in the oseltamivir-exposed group overall and 2.4% (7/284) in fetuses exposed to oseltamivir during the first trimester. Our study supports the idea that oseltamivir is not a major teratogen in humans.

The effect of zanamivir on birth defects is unclear. One paper documents 4 women who took zanamivir during pregnancy: 2 had healthy infants, 1 spontaneously miscarried, and 1 terminated the pregnancy.[12] Svensson's paper included 2 pregnant women who took zanamivir alone and 3 pregnant women who took oseltamivir and zanamivir.[14] But birth outcomes of these women were unknown. Our study showed a malformation rate of 0% (0/50) in the zanamivir-exposed group. One case of enlarged left adrenal gland in the zanamivir-exposed group was detected by ultrasonography before zanamivir exposure, but this condition had normalized in the infant at 1 year old. Therefore, we did not include this as a malformation case.

Generally, the rate of congenital abnormalities diagnosed up to the eighth month of life ranges from 2.2% to 3.0%,[23,24] although the rates in this study were 2.4% with in utero oseltamivir exposure and 0% with in utero zanamivir exposure. The results of this prospective study and 2 recent studies published after pandemic (H1N1) 2009[14,15] may provide reassurance when

TABLE 5

Pregnancy outcomes with exposure to antiinfluenza drugs according to drug type and timing of exposure

Variable	Outcomes with oseltamivir exposure			Outcomes with zanamivir exposure		
	1st trimeste	2nd trimester	3rd trimester	1st trimester	2nd trimester	3rd trimester
Number of outcomes	159	239	226	15	24	11
Miscarriage at <22 wks	2 (1.3) 0.2–4.5	1 (0.7) 0.0–4.1	—	0	0	—
Induced abortion	1 (0.6) 0.0–3.5	0	—	0	0	—
Stillbirth	0	0	0	0	0	0
Neonatal death	0	0	0	0	1 (4.2) 0.1–21.1	0
Preterm delivery<37 wks	6 (3.8)[a] 1.4–8.2	10 (4.2)[b] 2.0–7.6	13 (8.2)[c] 4.4–13.6	0	2 (8.3) 1.0–27.0	2 (25.0) 3.2–65.1
Low birthweight <2500 g	14 (9.0) 5.0–14.6	13 (5.5)[b] 2.9–9.2	26 (11.5) 7.7–16.4	1 (6.7) 0.2–31.9	3 (12.5) 2.7–32.4	1 (9.1) 0.2–41.3
Small for gestational age	12 (7.7) 4.0–13.1	17 (7.1)[b] 4.2–11.2	25 (11.1) 7.3–15.9	1 (6.7) 0.2–31.9	1 (4.2) 0.1–21.1	0
Infants with congenital anomalies	2 (1.3)	6 (2.5)	7 (3.1)	0	0	0
Congenital heart defect	1[d] (0.6) 0.0–3.5	5 (2.1)[b] 0.7–4.8	5 (2.2) 0.7–5.1	0	0	0
Deformity (excluding congenital heart defect)	1[e] (0.6) 0.0–3.5	1[f] (0.4)[b] 0.0–2.3	2[g] (0.9) 0.1–3.2	0	0	0
Infants with other adverse outcomes	6 (3.8) 1.4–8.2	9 (3.8)[b] 1.7–7.1	9 (4.0) 1.8–7.4	0	1 (4.2) 0.1–21.1	4 (36.4) 10.9–69.2
Infection	2 (1.3) 0.2–4.6	1 (0.4)[b] 0.0–2.3	0	0	0	0
Hyperbilirubinemia	0	2 (0.8)[b] 0.1–3.0	1 (0.4) 0.0–2.4	0	0	2 (18.2) 2.3–51.8
Hypoglycemia	1 (0.6) 0.0–3.5	1 (0.4)[b] 0.0–2.3	1 (0.4) 0.0–2.4	0	0	1 (9.1) 0.2–41.3
Transient tachypnea	3 (1.9) 0.4–5.5	2 (0.8)[b] 0.1–3.0	4 (1.8) 0.5–4.5	0	0	0
Respiratory distress syndrome	0	0	0	0	1 (4.2) 0.1–21.1	0
Pyrexia	0	1 (0.4)[b] 0.0–2.3	1 (0.4) 0.0–2.4	0	0	0
Hypothyroidism	1 (0.6) 0.0–3.5	0	1 (0.4) 0.0–2.4	0	0	0
Necrotizing enterocolitis	0	0	0	0	0	0
Intraventricular hemorrhage	0	0	0	0	0	0
Convulsion	0	0	1 (0.4) 0.0–2.4	0	0	0
Vomiting	1 (0.6) 0.0–3.5	0	0	0	0	0
Periventricular leukomalacia	0	1 (0.4)[b] 0.0–2.3	0	0	0	0
Hypernephroma	0	0	0	0	0	1 (9.1) 0.2–41.3

Data shown as number (%) 95% confidence interval.

AR, aortic regurgitation; *ASD*, atrial septal defect; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *TAPVR*, total anomalous pulmonary venous return; *VSD*, ventricular septal defect.

[a] Excluding 3 patients with miscarriage or induced abortion; [b] Excluding 1 patient with miscarriage; [c] Excluding 67 patients taking oseltamivir after week 37; [d] There were no cases of congenital heart defects or other deformities in infants exposed to oseltamivir or zanamivir during gestational weeks 4 to 7. In infants exposed during gestational weeks 8 to 14, the frequencies of congenital heart defects and other deformities were both 0.9% (1/113) with oseltamivir although there were no such defects or deformities with zanamivir. Details on congenital anomalies are shown in Table 5; [e] Hemangioma; [f] Cleft palate; [g] Agenesis of corpus collosum and Down syndrome complicated with VSD, AR, and PDA (Table 7).

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2009.

prescribing oseltamivir or zanamivir for pregnant women.

Greer et al[13] reported pregnancy outcomes after oseltamivir exposure during the first trimester in 18 women, the second trimester in 40 women, and the third trimester in 75 women. They found no increased rates of preterm births, fetal growth restriction, seizures, intraventricular hemorrhage, or hyperbilirubinemia, stating that "pregnant women treated with antiviral therapy for influenza were not dissimilar to those who did not have influenza antiviral exposure." The results of the current study support the statement by Greer et al[13] except for a case of necrotizing enterocolitis seen in 1 infant exposed to oseltamivir in their study. Statistical analysis indicated a higher frequency of necrotizing enterocolitis in infants exposed to oseltamivir in utero compared with those not exposed to oseltamivir (0.8% [1/133] vs 0.02% [14/79,549], $P < .001$).[2] However, none of the 620 infants exposed to oseltamivir developed necrotizing enterocolitis in this study. When our data, Svensson's data, and Greer's data were combined, the frequency of necrotizing enterocolitis in oseltamivir-exposed fetuses was 0.12% (1/859), and this ratio was not significantly higher than that in the unexposed fetuses (14/79,549) (odds ratio [OR], 6.62; 95% CI, 0.87–50.4). In Greer's report, the infant with necrotizing enterocolitis was born at 29 weeks and weighed 1200 g.[13] The necrotizing enterocolitis may have been the result of prematurity rather than exposure to oseltamivir, because prematurity is a strong risk factor for the development of necrotizing enterocolitis.[25] Svensson et al[14] recently reported that infants exposed to neuraminidase inhibitors in utero had a higher risk of late transient hypoglycemia (crude OR, 4.00; 95% CI, 1.26–12.76). In our study, hypoglycemia occurred in 3 (0.5%) of 620 oseltamivir-exposed infants and 1 (2.0%) of 50 zanamivir-exposed infants. When our data and Svensson's data were combined, the frequency of hypoglycemia in the neuraminidase-exposed group was 1.0% (8/780), which was lower than that in the unexposed group in Svensson's report (1.2%; 10/860).

TABLE 6
Details of adverse birth outcomes in 29 infants

Case no.	Gestational week at exposure	Gestational week at delivery	Birthweight, g	Drug	Adverse birth outcomes
1	8	39	3272	Oseltamivir	Vomiting
2	11	38	2795	Oseltamivir	TTN, sepsis suspected
3	12	36	3108	Oseltamivir	TTN
4	12	40	2612	Oseltamivir	Hypothyroidism
5	13	36	2424	Oseltamivir	Hypoglycemia
6	13	38	3100	Oseltamivir	TTN
7	14	37	2280	Oseltamivir	TTN
8	15	31	1794	Oseltamivir	PVL
9	16	39	3000	Oseltamivir	Small intestinal obstruction
10	17	41	3025	Oseltamivir	Fever
11	19	40	2584	Oseltamivir	Hyperbilirubinemia
12	19	37	2670	Oseltamivir	TTN
13	23	37	3056	Oseltamivir	Hypoglycemia
14	23	40	2916	Oseltamivir	Infection
15	24	24	662	Zanamivir	TTN
16	24	39	3238	Oseltamivir	Hyperbilirubinemia
17[a1]	28	36	1950	Oseltamivir	TTN
18[a1]	28	36	1768	Oseltamivir	TTN
19	30	35	2285	Oseltamivir	TTN
20[a2]	31	35	2390	Oseltamivir	Hyperbilirubinemia
21[a2]	31	35	2104	Oseltamivir	Hypoglycemia
22	32	33	2244	Zanamivir	Hypoglycemia
23	32	37	2984	Zanamivir	Hyperbilirubinemia
24	34	39	3170	Oseltamivir	TTN
25	35	36	2060	Oseltamivir	Hypothyroidism
26[b]	36	38	3245	Oseltamivir	Convulsion, agenesis of the corpus collosum
27	36	39	3392	Zanamivir	Hypernephroma (left)
28	37	38	3572	Oseltamivir	Fever
29	38	39	3294	Zanamivir	Hyperbilirubinemia

PVL, periventricular leukomalacia; *TTN*, transient tachypnea of the newborn.

[a] Twins, 2 cases of twin pregnant cases were presented: case no. 17 and 18, and case no. 20 and 21 were pair cases; [b] Alcohol use case.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

Implications for clinicians

The results from this study suggest that clinically effective doses of oseltamivir do not have the potential to produce adverse effects on human fetal development. The data available until now have been limited, but our data lend support to the safety of oseltamivir in pregnancy. Oseltamivir exposure did not increase the incidence of adverse pregnancy outcomes such as miscarriage, preterm delivery, stillbirth at

TABLE 7
Details of congenital anomalies in 14 infants

Case no.	Gestational week at exposure	Gestational week at delivery	Birthweight, g	Drug	Congenital anomalies
1	9	39	3120	Oseltamivir	ASD, PS
2	11	37	2306	Oseltamivir	Hemangioma
3	14	39	2948	Oseltamivir	VSD
4	18	39	2760	Oseltamivir	VSD
5	21	40	2640	Oseltamivir	Cleft palate
6	22	38	3050	Oseltamivir	VSD
7	22	39	2682	Oseltamivir	VSD
8	27	41	3205	Oseltamivir	ASD
9	30	39	2830	Oseltamivir	ASD, VSD, bicuspid aortic valve
10	33	39	2880	Oseltamivir	Down syndrome, VSD, AR, PDA
11	34	39	2898	Oseltamivir	TAPVR
12	36	40	3165	Oseltamivir	VSD
13	36	38	3245	Oseltamivir	Convulsion, agenesis of the corpus collosum
14	37	41	3000	Oseltamivir	Complete TGA

AR, aortic regurgitation; *ASD*, atrial septal defect; *PDA*, patent ductus arteriosus; *PS*, pulmonary stenosis; *TAPVR*, total anomalous pulmonary venous return; *VSD*, ventricular septal defect.

Saito. Oseltamivir or zanamivir exposure during H1N1 2009. Am J Obstet Gynecol 2013.

or after 22 weeks, neonatal death, birthweight <2500 g, small-for-gestational-age infants, necrotizing enterocolitis, intraventricular hemorrhage, seizures, and other transient abnormalities in the neonatal period. As similar findings have also been reported,[12-15] our data reinforce the idea that the benefits of oseltamivir treatment for influenza in pregnant women outweigh the risks. Although the sample number is too small (n = 50), the safety of zanamivir treatment during pregnancy seems to be supported by our study.

The WHO and CDC recommended treatment for all high-risk patients, including pregnant women, and the European Medicines Agency advises that the benefit of treating pregnant women with antiviral drugs outweighs the risk.[2,3,26] Our data suggest that oseltamivir treatment during pregnancy is unlikely to cause adverse pregnancy or fetal outcomes, although more data are necessary to reach a definitive conclusion.

Strengths and limitations of study

The sample numbers of oseltamivir-exposed pregnant women (n = 619) and zanamivir-exposed pregnant women (n = 50) in this study were much larger than those in previous studies. The present data corroborates the safety of oseltamivir and zanamivir for fetuses and pregnant women.

A limitation to the generalizability of our study is that we examined only the short-term prognosis of the infants. To clarify the long-term prognosis of infants exposed to antiviral drugs, the infants must be followed-up until 2 years old.

Also, miscarriages are more common in early pregnancy; therefore, the fact that many women were not registered in this study until after this period make it difficult to draw conclusive comparisons with miscarriage rates in the general population.

Conclusion

The early use of oseltamivir and zanamivir is thought to have contributed to the absence of maternal mortality from pandemic (H1N1) 2009 in Japan.[5,6] Given the results of this study as well as previous studies,[12-15,27] we believe that oseltamivir and zanamivir during pregnancy does not adversely affect pregnancy outcome. ■

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LETTERS TO THE EDITOR

Causes of a nationwide rubella outbreak in Japan, 2012–2013

Dear Editors,

Although rubella can lead to severe encephalitis,[1] rubella infection is usually mild among children. However, rubella in pregnant women can cause congenital rubella syndrome (CRS) as a devastating consequence. Although congenital rubella syndrome (CRS) is a preventable disease with universal immunization, as many as 13 newborns contracted CRS in the nine months from October 2012 to July 2013 (1.5 per 100,000 live births) in Japan as a consequence of a rubella epidemic (Fig. 1). In this outbreak, the majority of cases of rubella occur among adult males[2]; among 11,489 patients (88 per 1.0 million) reported during the first six months of 2013, 8845 (77%) were males and 8059 (70%) were males 20 years of age or more.[2] As we experienced a rubella epidemic nine years ago in 2004, in which 10 infants were diagnosed with CRS, we knew what measures would be effective to prevent a rubella epidemic at that time. Therefore, the current disaster was predictable and may have been avoided if appropriate measures had been implemented.

In 1976, Japan introduced a single-antigen rubella vaccine to the national immunization program targeting girls in junior high school. Between 1989 and 1993, a measles–mumps–rubella (MMR) vaccine was targeted toward children 12–36 months of age. Since 1995, the single-antigen rubella and measles–rubella (MR) vaccines have been strongly recommended for children 12–90 months of age as a standard immunization; however the program is not mandatory. Although a supplemental vaccination campaign was conducted to increase population immunity, the vaccine coverage rate was too low, and adult males remain susceptible to rubella (Fig. 2). There are approximately 1.05–1.1 million annual births in Japan, and only one infant contracted CRS each year from 2000 to 2003. However, this period was followed by a rubella outbreak in 2004 in which 10 infants became infected with CRS. According to a population immunity survey that was strengthened after the rubella epidemic in 2004 and has been conducted yearly since 2006, the number of persons without immunity against rubella (less than 1:8 on an hemagglutination inhibition assay, HI test) is consistently higher among male than female adults 20–49 years of age, with a difference of approximately 7–22 points (%) in 2006 and 2012 (Fig. 2).[3]

In 2004, the Japanese Ministry of Health, Labour and Welfare (JMHLW) announced the following three emergency strategies to control the rubella epidemic[4]: the development of a vaccination campaign, including a strong recommendation for rubella vaccination among the family members of pregnant females, adult females and postpartum females, and an increase in the vaccine coverage rate for the standard immunization program; guidance for the creation of appropriate diagnostic procedures for managing rubella infection in pregnancy and prenatal screening of CRS; and the establishment of a new surveillance system to monitor rubella infection that requires all physicians to report any clinically and/or laboratory confirmed rubella cases.[4] However, male adults were not included as targeted subjects, and vaccination was not mandatory, even for the targeted population. The annual number of subjects who received supplementary vaccination under this program is estimated to be 270,000, 330,000 and 260,000 in fiscal years 2009, 2010 and 2011, respectively, according to the JMHLW,[5] while the population of Japan is approximately 130 million people. As the proportion of pregnant females susceptible to rubella (less than 1:8 on an HI test) in Tokyo was 6.7% in 2003–2006,[6] the campaign decreased the fraction of the population that is susceptible to rubella among female adults by approximately 3% and male adults by approximately 5% (Fig. 2); however, a rubella outbreak occurred again in 2012–2013. Among the individuals affected in the current epidemic, the vaccination history was unknown in a majority of patients (7393 [64%]). Among the 4096 patients with a known vaccination status, 3366 (82%) cases occurred in persons who had not received the rubella vaccine.[2] Based on the data shown in Fig. 2, we estimate that approximately 5.1 million adult males 20–49 years of age were susceptible to rubella in 2006 (the population of males in the 20s, 30s and 40s totaled approximately 7.6, 9.4 and 7.8 million, respectively, in Japan in 2006). The rubella outbreak and CRS infections occurred in the presence of a high vaccination coverage rate among females, with a low coverage rate in some populations in the community.[7–9] Therefore, the current rubella epidemic was predictable. In order to achieve rubella elimination within several years after the time of the previous rubella outbreak, it was necessary to provide supplementary vaccination to more than 1.0 million male adults each year for the first several years.

As of October 2010, the WHO Region of the Americas and European Regions established rubella elimination goals for the years 2010 and 2015, respectively, while the Western Pacific Region has established targets for achieving

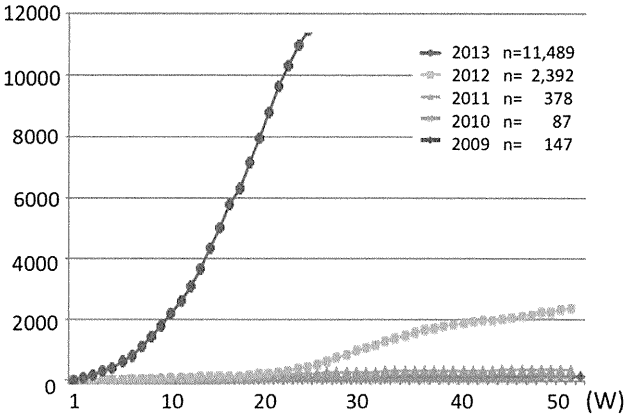

Figure 1 Cumulative number of rubella patients by week, 2009–2013 (as of June 26, 2013).[1]

accelerated rubella control and CRS prevention goals (an incidence of less than 1.0 per 100,000 live births).[10] Programs to eliminate rubella have indeed been successful in the USA[11] and appear to be successful in some European countries.[12,13] In July 2013, three groups, including the Japan Society of Obstetrics and Gynecology, Japan Association of Obstetricians and Gynecologists and Japan Society of Perinatal and Neonatal Medicine, asked the JMHLW to establish a distinctive policy for eliminating rubella and providing an emergency strategy to overcome the shortage of vaccines in the current outbreak.[14] If effective measures regarding a vaccination program targeting male adults are not taken, it may not be possible to suppress the current rubella epidemic, and more patients will develop CRS. In addition, newborns with CRS continue to shed the infectious virus for several months,[15] acting as a source of the rubella virus and a possible trigger of future rubella outbreaks. We fear exporting rubella to WHO Regions of the Americas and Europe, where health care providers are struggling to achieve and sustain a rubella vaccine coverage rate of ≥95% among the general population in order to eliminate rubella,[11–13] and developing countries, in which national vaccination programs have not been implemented.

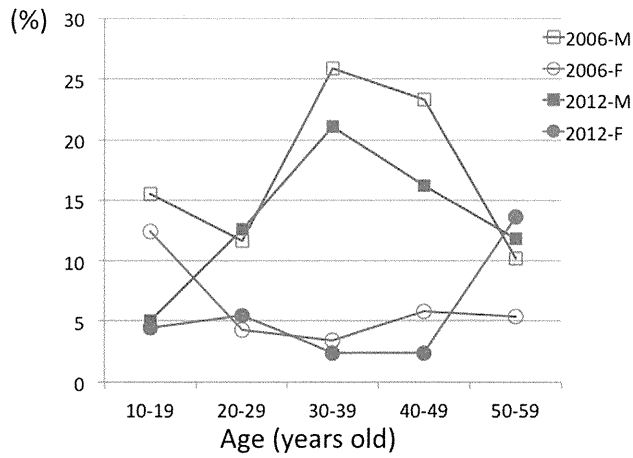

Figure 2 Rates of male and female Japanese individuals who were susceptible to rubella in 2006 and 2012 according to age. The rectangles and circles indicate males and females, respectively. Immunity against rubella was determined using the hemagglutination inhibition test. Persons with a test result of less than 1:8 were judged as being susceptible to rubella. The data were obtained from the website of the National Institute of Infectious Disease (Japan)(cited July 8, 2013 from the URL: http://www.nih.go.jp/niid/ja/y-graphs/3373-rubella-yosoku-serum2012.html and the URL: http://www.nih.go.jp/niid/ja/y-graphs/1917-rubella-yosoku-serum2006.html).

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