ブロークン・ハート:
妊娠中のSSRIs

Broken Hearts:
SSRIs in Pregnancy

デレリー・マンギン
Derelie Mangin
June 2010
Medwatcher Japan Symposium
Drug Safety and Drug Companies
Marketing

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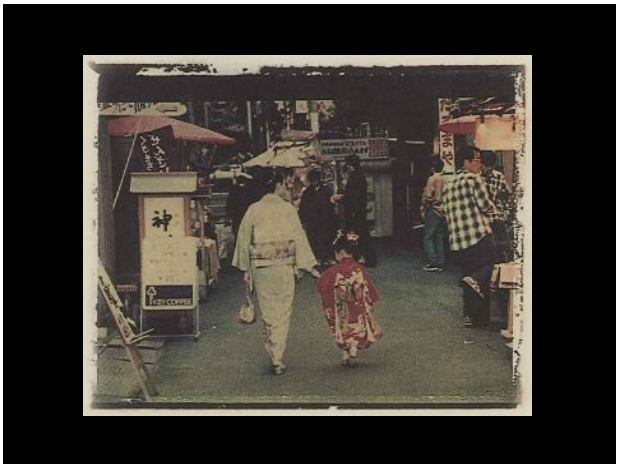

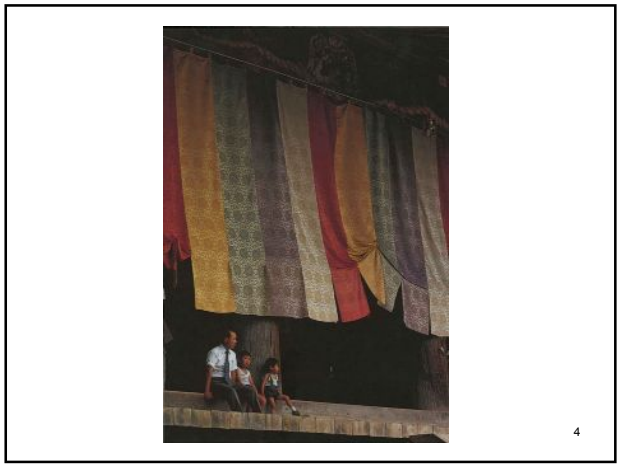

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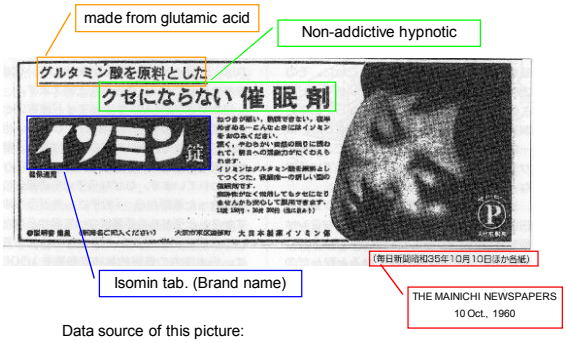
1960年10月10日　毎日新聞　イソミン錠（サリドマイド）の広告記事

News paper advertisement for thalidomide tablets: Isomin tab.



Data source of this picture:

http://d-inf.org/drug/thalidomide.html

サリドマイド 1962

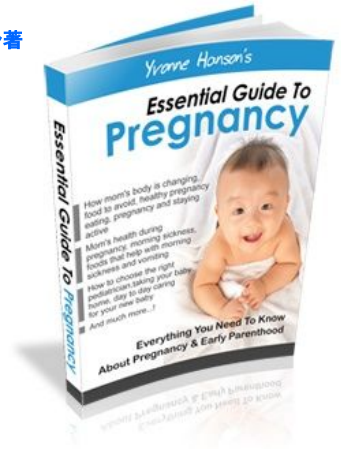
Thalidomide 1962

“FDAはなぜ、このような恐ろしい事実を発見するのに長い時間をかけ、サリドマイドを市場から撤退させるのに1年も待ったのか？”

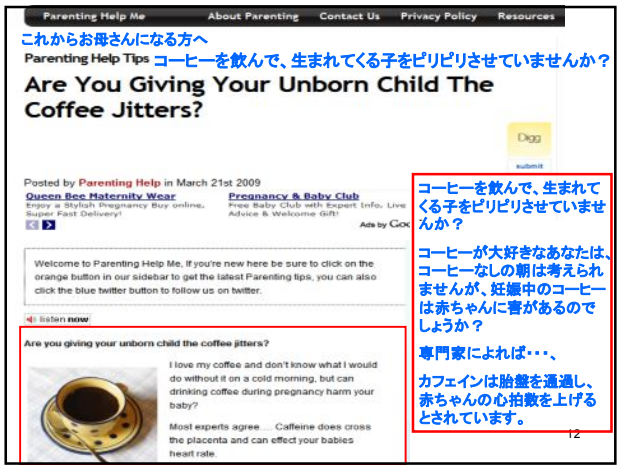
“ Why did the FDA take so long to make these horrific discoveries, and why did they wait almost a year to get them off the market?”

イボンヌ・ハンソン著

「妊娠ガイド」



妊娠中の食事では、何を食べるかと同じくらい、何を食べてはいけないかが大切です。食べ物の中には、あなたの赤ちゃんにもあなた自身にも害になるものがあるので、安全であることが第一です。妊娠中のあなたは、つぎに示すものは食べないようにしましょう。



これからお母さんになる方へ

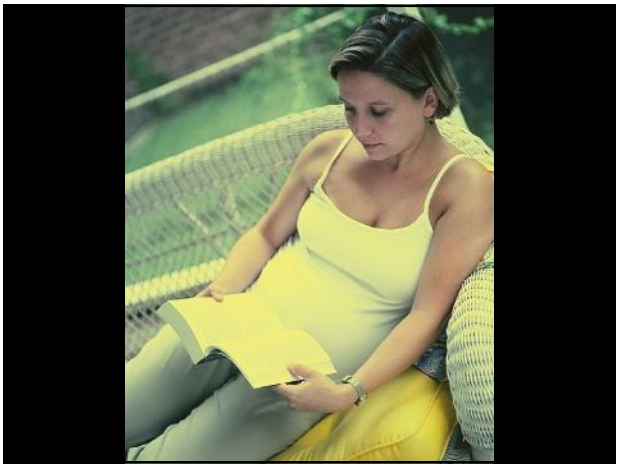
Parenting Help Tips コーヒーを飲んで、生まれてくる子をピリピリさせていませんか？

コーヒーを飲んで、生まれてくる子をピリピリさせていませんか？

コーヒーが大好きなあなたは、コーヒーなしの朝は考えられませんが、妊娠中のコーヒーは赤ちゃんに害があるのでしょうか？

専門家によれば・・・、

カフェインは胎盤を通過し、赤ちゃんの心拍数を上げるとされています。



パキシル錠
Paxil tab.

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STUDY 295 1979	試験295 1979
415 Rat Pups Born 368 Viable 47 born Dead	生まれたラットの子供 415匹中 出生時 生存 368匹 死亡 47匹
パキシル 投与量 Paxil Dose	4日目までに死亡したラット % %Dead @ 4 Days
0 mg	12%
5 mg	66%
15 mg	92%
50 mg	100%

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雑誌「生殖毒性」2009年掲載 論文

12のモノアミン再取り込み阻害剤に関する生殖毒性（試験管内実験および動物実験）：稀に発生する心血管系奇形のメカニズム

Accepted Manuscript

Title: *In vitro* and *in vivo* reproduction toxicology of 12 monoaminergic re-uptake inhibitors: Possible mechanisms of infrequent cardiovascular anomalies

Authors: Willem N. Sloot, H. Clare Bowden, Tjong D. Yih

PII: S0890-6238(09)00096-3
DOI: doi:10.1016/j.reprotox.2009.04.005
Reference: RTX 6259

To appear in:

Received date: 2-3-2009
Revised date: 10-4-2009
Accepted date: 10-4-2009

ニューイングランド ジャーナル オブ メディシン 1996年掲載論文

標題: フルオキセチン内服妊婦における出産結果

結論: 妊娠中のフルオキセチンで自然流産や大奇形(major anomaly) のリスクは高くならないが、妊娠第3三半期に内服した場合は、小奇形(minor anomaly) や呼吸障害などの出生時異常を増やす。

The New England Journal of Medicine

BIRTH OUTCOMES IN PREGNANT WOMEN TAKING FLUOXETINE

CHRISTINA D. CHAMBERS, B.A., KATHLEEN A. JOHNSON, B.A., LYN M. DICK, B.A., ROBERT J. FELIX, B.A., AND KENNETH LYONS JONES, M.D.

ABSTRACT

Background Although fluoxetine is the most frequently prescribed antidepressant drug in the United States, its safety in pregnant women has not been established.

Methods From 1989 through 1995, we prospectively identified 228 pregnant women taking fluoxetine. We compared the outcomes of their pregnancies with those of 254 women identified in a similar manner who were not taking fluoxetine.

Results The rate of spontaneous pregnancy loss did not differ significantly between the women treated with fluoxetine and the control women (10.5 percent and 9.1 percent, respectively), nor was the rate of major structural anomalies significantly different (5.5 percent vs. 4.0 percent). Among the 97 infants exposed to fluoxetine who were evaluated for minor anomalies, the incidence of these or more minor anomalies was significantly higher than among 153 similarly examined control infants (15.9 percent vs. the basis of cases from the same data base, there was no increase in perinatal complications in 112 women who took fluoxetine during the third trimester. However, these data are difficult to interpret in the absence of a comparison group and given the high proportion of pregnancies (37%, or 82.6 percent of those prospectively ascertained) for which there was no information about outcome.

Between 1988 and 1992, the Michigan Medicaid surveillance program identified 1.09 infants whose mothers had received fluoxetine during pregnancy. The rate of major anomalies in the infants (1.8 percent) did not exceed the expected rate of 3 to 4 percent. In another study of 128 women who received fluoxetine during the first trimester of pregnancy, there was no greater incidence of structural anomalies or perinatal complications than in pregnant women who received tricyclic antidepressant drugs.

Our study was undertaken to determine the ef

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1996

1994

日本の厚生労働省は、GSKに対し生殖毒性の追加試験を要求
これに対してGSKは次のように反応した:
"GSKとしては避けたい試験を、しかも厚労省が望ましいと考える研究デザインで行うように、指示・強要されるかもしれない。"

Request from the Japanese regulatory authority to GSK for further studies on reproductive safety

"The MHW [may] request us to do the type of study we wish to avoid. If they do request a study, there is a potential problem in that they may direct/insist on our performing a study to their preferred design."

GSK response

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"妊娠中にパロキセチンを内服した520人中、出生時の結果が判明した313人について見てみると、42例(13.3%: 42/313)に先天異常報告あり"

"313 pregnancies with a known outcome [out of 520 patients receiving paroxetine during pregnancy] there have been 42 reports (13.3%) of pregnancy in which a congenital abnormality was reported"

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2005

GSKは妊娠中の危険性を調査するための疫学研究は1つも実施していなかった。

GSK had not done a single epidemiological study to investigate the risks in pregnancy

グラクソによる粉ミルクの広告「健康な赤ちゃんを育てる食品」

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パキシルによる先天異常 Birth Defects

年 著者	オッズ比	
1998 Kulin	1.8	⬆
2002 Simon	0.7	
2003 Casper	2.4	⬆
2005 Diav Citrin	1.9	⬆
2005 Malm	0.9	
2006 Vial	1.4	⬆
2006 Wen	1.3	⬆
2006 Schloemp	0.8	
2007 Davis	1.0	⇨
2007 Alwan	11.6	⬆
2007 Berard	1.3	⬆
2007 Cole	1.9	⬆
2007 Kallen	1.0	⇨
2007 Louik	1.4	⬆
Chambers (unpub)	5.1	⬆

15の疫学研究 個々の結果
⬆ 先天異常リスク上昇
⇨ 先天異常リスク変わらず

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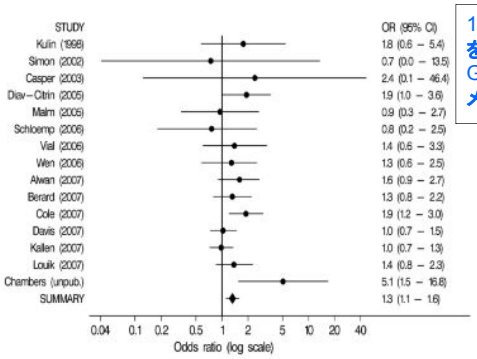
パキシルによる先天異常: 妊娠初期12週間内服
Birth Defects: first 12 weeks



15の疫学研究を用いた、GSK社によるメタアナリシス

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パキシルによる心奇形: 妊娠初期12週間内服
Heart Defects

1998 Kulin	0.8	
2005 Diav Citrin	3.5	⬆
2005 Malm	0.7	
2006 Bakker	1.5	⬆
2006 Vial	1.2	⬆
2007 Davis	1.0	⇨
2007 Alwan	1.7	⬆
2007 Berard	1.4	⬆
2007 Cole	1.5	⬆
2007 Kallen	1.6	⬆
2007 Louik	1.4	⬆
Chambers (unpub)	10.8	⬆
Nash (unpub)	0.4	

13の疫学研究 個々の結果
⬆ 先天異常リスク上昇
⇨ 先天異常リスク変わらず

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パキシルによる心奇形: 妊娠初期12週間内服
Heart Defects

1998 Kulin	0.8	
2005 Diav Citrin	3.5	⬆
2005 Malm	0.7	
2006 Bakker	1.5	⬆
2006 Vial	1.2	⬆
2007 Davis	1.0	⇨
2007 Alwan	1.7	⬆
2007 Berard	1.4	⬆
2007 Cole	1.5	⬆
2007 Kallen	1.6	⬆
2007 Louik	1.4	⬆
Chambers (unpub)	10.8	⬆
Nash (unpub)	0.4	

13の疫学研究 個々の結果
⬆ 先天異常リスク上昇
⇨ 先天異常リスク変わらず

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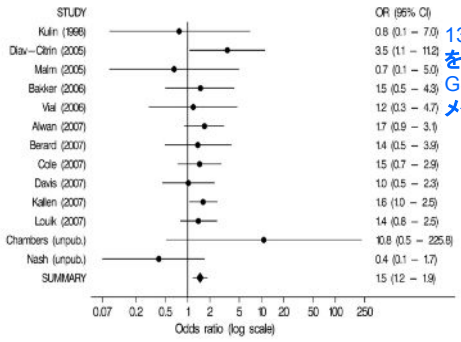
心奇形: 妊娠初期12週間
Heart Defects: first 12 weeks



13の疫学研究を用いた、GSKによるメタアナリシス

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英国医師会雑誌2009年掲載論文「妊娠中のSSRIと先天異常: 大規模コホート研究」

BMJ RESEARCH

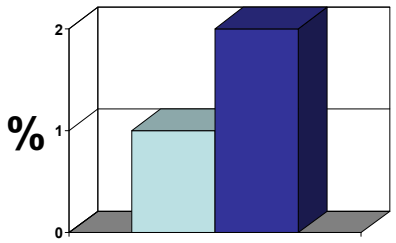
Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study

結果よりResults:

妊娠中のSSRIと出生児の心房/心室中隔欠損
SSRI in pregnancy and septal heart defects

SSRIなし unexposed children	0.5%
SSRI服用 children whose mothers were prescribed any SSRI	0.9%
2種類以上SSRI服用 children whose mother were prescribed more than one type of SSRI	2.1%

心奇形のリスク
Risk of Heart Defects



パキシル
Paxil

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葉酸補充による
先天性神経管閉鎖障害リスクの低下

1/1000

1/4000

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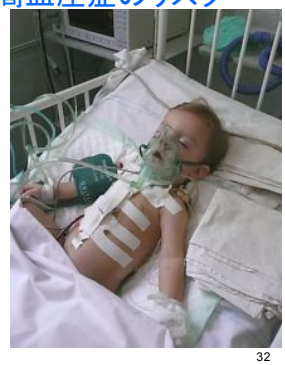
妊娠中のSSRIによる
新生児遷延性肺高血圧症のリスク

1/100 ⟹ 1/50



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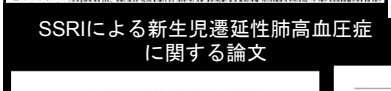
SSRIによる新生児禁断（離脱）症候群に関する論文


Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis


Effects of Antenatal Depression and Antidepressant Treatment on Gestational Age at Birth and Risk of Preterm Birth

SSRIによる新生児遷延性肺高血圧症に関する論文


Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn


Perinatal Outcome Following Third Trimester Exposure to Paroxetine

- 早産 (12% vs 5%)
- 新生児離脱（禁断）症候群 (SSRI曝露児の20-30%)
  - 呼吸窮迫症状, チアノーゼ, 痙攣, 神経過敏, 泣き続ける, 哺乳障害, 嘔吐
- 新生児遷延性肺高血圧症
  - 妊娠20週以降のSSRI内服でリスクが6倍に
  - 死亡率10-20%
- 自然流産 (14% vs 9%)
- 人工流産 (7% vs 4%)

- **Premature birth** (12% vs 5%)
- **Neonatal Withdrawal Syndrome** (20-30% exposed)
  Respiratory distress, cyanosis, seizures, jitteriness, constant crying, difficulty feeding, vomiting
- **Persistent Pulmonary Hypertension of the Newborn**
  6x increase with SSRI use after 20 weeks
  10-20% mortality
- **Spontaneous Miscarriages** (14% vs 9%)
- **Voluntary Abortions** (7% vs 4%)

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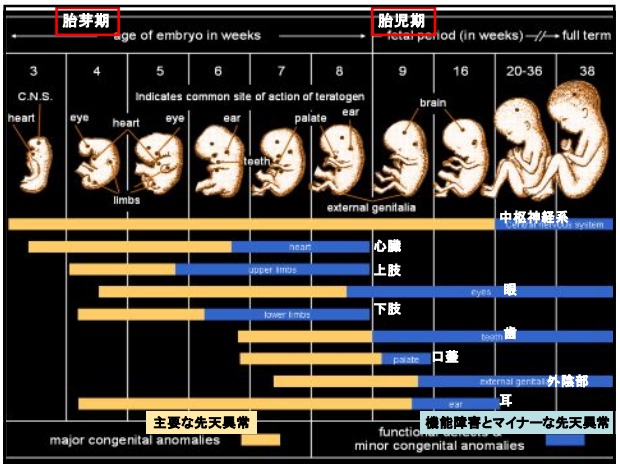

胎内で三環系抗うつ剤またはフルオキセチンに曝露された児の発達: 前向き比較研究

Child Development Following Exposure to Tricyclic Antidepressants or Fluoxetine Throughout Fetal Life: A Prospective, Controlled Study

結果より: 三環系抗うつ剤、フルオキセチンともに、児のIQ、言語発達、行動に対する害作用はなかった。児のIQと母親のうつ状態の期間との間には有意な負の関係が認められたが、言語発達は、出産後のうつ発作回数との関連が認められた。

結論: 妊娠期から産後にかけての抗うつ剤治療は、必要に応じて行われることが望ましい。


Objective: Previous work suggested that first-trimester exposure to tricyclic antidepressants or fluoxetine does not affect adversely child IQ and language development. However, many women need antidepressants throughout pregnancy to avoid morbidity and suicide attempts. Little is known about the fetal safety of tricyclic antidepressants and fluoxetine when taken throughout pregnancy. The goal of this study was to assess the effects of tricyclic antidepressants and fluoxetine used throughout gestation on child IQ, language, and behavior.

Method: In a prospective study, mother-child pairs exposed throughout gestation to tricyclic antidepressants (N=46) or fluoxetine (N=40) and an unexposed, not depressed comparison group (N=54) were blindly assessed. The three groups were compared in terms of the children's IQ, language, behavior, and temperament between ages 15 and 71 months. The authors adjusted for independent variables such as duration and severity of maternal depression, duration of pharmacological treatment, number of depression episodes after delivery, maternal IQ, socioeconomic status, cigarette smoking, and alcohol use.

Results: Neither tricyclic antidepressants nor fluoxetine adversely affected the child's global IQ, language development, or behavior. IQ was significantly and negatively associated with duration of depression, whereas language was negatively associated with number of depression episodes after delivery.

Conclusions: Exposure to tricyclic antidepressants or fluoxetine throughout gestation does not appear to adversely affect cognition, language development, or the temperament of preschool and early-school children. In contrast, mothers' depression is associated with less cognitive and language achievement by their children. When needed, adequate antidepressant therapy should be instituted and maintained during pregnancy and postpartum.

(Am J Psychiatry 2002; 159:1889–1895)

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米国小児科学会雑誌　PEDIATRICS
2010年2月22日online掲載論文

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

胎児期の抗うつ剤曝露と生後6ヶ月時点と19ヶ月時点における正常発達のマイルストーン

Fetal Exposure to Antidepressants and Normal Milestone Development at 6 and 19 Months of Age

Lars Henning Pedersen, Tine Brink Henriksen and Jorn Olsen
Pediatrics published online Feb 22, 2010;
DOI: 10.1542/peds.2008-3655

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胎児期の抗うつ剤曝露と生後6ヶ月時点と19ヶ月時点における正常発達のマイルストーン

Fetal Exposure to Antidepressants and Normal Milestone Development at 6 and 19 Months of Age

WHAT'S KNOWN ON THIS SUBJECT: In animals, antidepressant exposure in early life causes changes that persist into adulthood. Results from human studies have been equivocal and either found no association between antidepressants and fetal brain development or suggested subtle effects on fine motor development.

WHAT THIS STUDY ADDS: We found associations between exposure to antidepressants in late pregnancy and motor development, particularly for boys. The clinical and public health relevance of the results is not known, and longer follow up monitoring of the children is needed.

AUTHORS: Lars Henning Pedersen, MD, PhD,[a,b] Tine Henriksen, MD, PhD,[c] and Jørn Olsen, MD, PhD[d]
[a]Department of Epidemiology, Institute of Public Health, University, Aarhus, Denmark; Departments of [b]Obstetrics Gynecology and [c]Pediatrics, Aarhus University Hospital, Denmark; and [d]Department of Epidemiology, School of P Health, University of California, Los Angeles, California

KEY WORDS
neurobehavioral behavior, selective serotonin reuptake inhibitor, prenatal exposure, serotonin

ABBREVIATIONS
TCA—tricyclic antidepressant
SSRI—selective serotonin reuptake inhibitor
OR—odds ratio

新しい知見: 妊娠後期における抗うつ剤曝露が、男児での運動機能発達と関連していた。臨床的に、また公衆衛生上、この問題がどの程度重要かはまだ不明であり、母体内で抗うつ剤に曝露した児の長期観察が必要である。

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胎児期の抗うつ剤曝露と生後6ヶ月時点と19ヶ月時点における正常発達のマイルストーン

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[a]Department of Epidemiology, Institute of Public Health, A University, Aarhus, Denmark; Departments of [b]Obstetrics Gynecology and [c]Pediatrics, Aarhus University Hospital, A

CONCLUSION: The results of this study suggest a permanent or reversible effect of antidepressant exposure on fetal brain development, which may depend on the timing of exposure during pregnancy.
Pediatrics 2010;125:e600–e608

結論: この研究の結果は、妊娠中における抗うつ剤曝露が、胎児の脳の発達に不可逆的または可逆的影響を及ぼし、その影響は妊娠中の曝露のタイミングと関係していることを示唆している。

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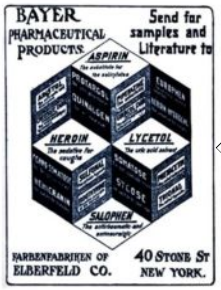
バイエル社の広告

ヘロイン



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SSRIからの離脱
Stopping SSRIs

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SSRI 離脱（退薬）症状
SSRI Withdrawal Symptoms

めまい,眩暈, 吐き気, 倦怠感,
頭痛, 不安, 不穏, 不眠,
易刺激性,静坐不能, 電気刺激様感覚,
そしておそらく, 攻撃的・衝動的行動も….

Dizziness, vertigo, nausea, fatigue, headache, anxiety, agitation, insomnia, irritability, akathisia, electric shock-like sensations, and possibly, aggressive and impulsive behaviour….

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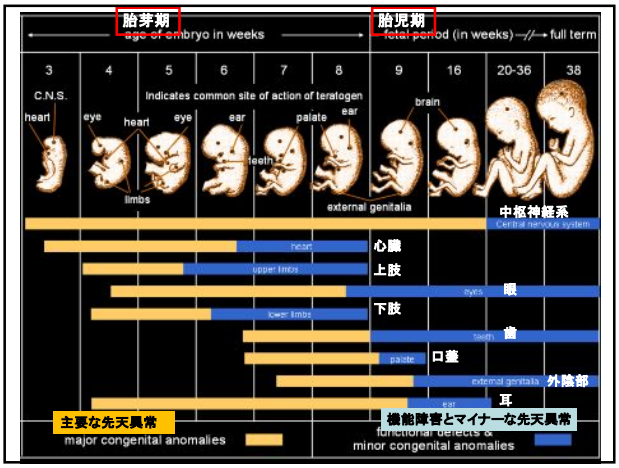

パキシル製剤 ラベルの記載
2005

FDA: 妊娠期のリスク･カテゴリー - D
妊娠期の使用: 催奇形作用: 疫学研究では、妊娠第1三半期にパロキセチンに曝露された胎児では、先天異常、特に心血管系で異常が発生するリスクが高くなることが示されている。この薬を妊娠中に使用する場合は、胎児へのリスクを考慮してもなお、使用が正当化される場合にのみ使用することが望ましい。

FDA: Pregnancy Category - D
Usage in Pregnancy: *Teratogenic Effects:* Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations… this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Paxil product label 2005

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グラクソによる 粉ミルクの広告

健康な子供を育てる食品

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GSK グラクソ･スミスクライン株式会社

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STUDY 295 1979	試験295 1979
415 Rat Pups Born 368 Viable 47 born Dead	生まれたラットの子供 415匹中 出生時 生存 368匹 死亡 47匹
パキシル 投与量 Paxil Dose	4日目までに死亡したラット % %Dead @ 4 Days
0 mg	12%
5 mg	66%
15 mg	92%
50 mg	100%

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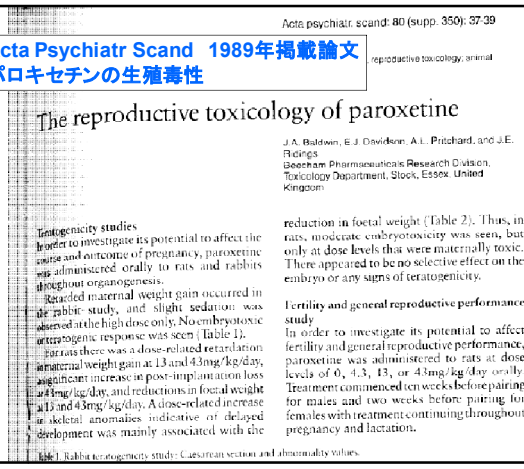
Acta Psychiatr Scand 1989年掲載論文
パロキセチンの生殖毒性


Acta psychiatr. scand. 80 (supp. 350): 37-39

reproductive toxicology; animal

The reproductive toxicology of paroxetine

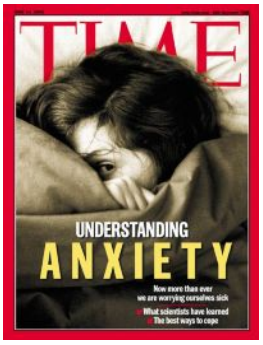
J.A. Baldwin, E.J. Davidson, A.L. Pritchard, and J.E. Riding
Beecham Pharmaceuticals Research Division, Toxicology Department, Stock, Essex, United Kingdom

1989

Teratogenicity studies
In order to investigate its potential to affect the course and outcome of pregnancy, paroxetine was administered orally to rats and rabbits throughout organogenesis.
Retarded maternal weight gain occurred in the rabbit study, and slight sedation was observed at the high dose only. No embryotoxic or teratogenic response was seen (Table 1).
For rats there was a dose-related retardation in maternal weight gain at 13 and 43mg/kg/day, a significant increase in post-implantation loss at 43mg/kg/day, and reductions in foetal weight at 13 and 43mg/kg/day. A dose-related increase in skeletal anomalies indicative of delayed development was mainly associated with the reduction in foetal weight (Table 2). Thus, in rats, moderate embryotoxicity was seen, but only at dose levels that were maternally toxic. There appeared to be no selective effect on the embryo or any signs of teratogenicity.

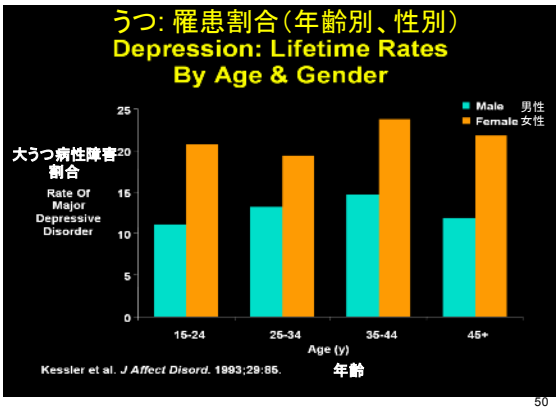
Fertility and general reproductive performance study
In order to investigate its potential to affect fertility and general reproductive performance, paroxetine was administered to rats at dose levels of 0, 4.3, 13, or 43mg/kg/day orally. Treatment commenced ten weeks before pairing for mates and two weeks before pairing for females with treatment continuing throughout pregnancy and lactation.

Table 1. Rabbit teratogenicity study: Caesarean section and abnormality values.



不安を知る

ストレス！
現代不安の治療法を探す



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- 催奇形性に関する初期の警告サインを無視
- 先天障害、その他の異常に関するデータが公表された場合は、その因果関係を否定する
- 規制当局に対しては、これらの異常に関するデータの提供を避ける
- うつ病を治療しないことによる危険性を論拠に、妊娠可能年齢の女性に対し、パキシルを使用するよう積極的な宣伝活動
- Ignored the early warning signs of teratogenic effects
- Denied causality when the data on birth defects and other problems became public
- Avoided supplying data to regulators regarding these effects
- Actively promoted of Paxil to women of child-bearing age on the basis of the risks of untreated depression

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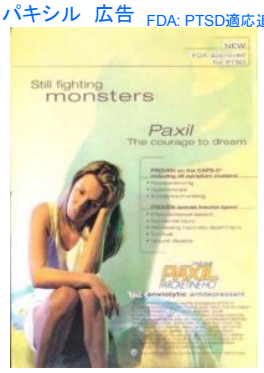
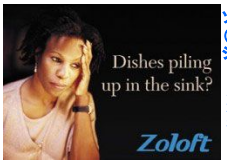
パキシル　広告　FDA: PTSD適応追加



まだモンスターとの格闘を続けるつもり？パキシルは、あなたに夢見る勇気を与えます



ゾロフト 広告
（日本製品名ジェイゾロフト）

流しに山積みになっているお皿をどうしよう？

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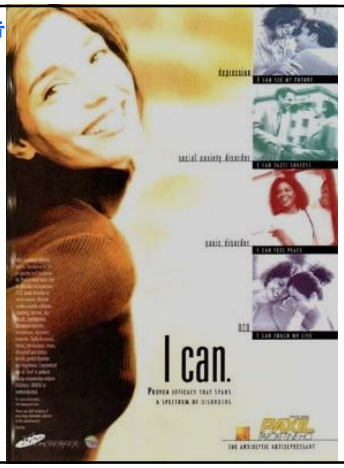
パキシル広告



うつ
depression

社会不安障害
social anxiety disorder

パニック障害
panic disorder

強迫神経症
OCD

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ゾロフト（日本製品ジェイゾロフト） キャシーの場合

娘はこう言いました。「ママはもう、以前の楽しいママじゃないんだね。」

それを聞いて私は、なんとかしなきゃいけないと思いました。

インターネットで調べると、ゾロフトが同類の薬の中では一番処方されていることがわかりました。

主治医にゾロフトのことを訊いてみると、いいと思いますよと言って、処方してくれました。

（のみ始めて）まもなく、変化が現れたのが私にはわかりましたし、家族にもそうでした。

"You get one chance to raise your kids, why do it with depression?"

"わが子を育てるチャンスは一度っきり，うつ病を抱えて子育てするつもり?"

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パキシル製剤 ラベルの記載 2005

FDA: 妊娠期のリスク･カテゴリー - D

妊娠期の使用：催奇形作用：疫学研究では、妊娠第1三半期にパロキセチンに曝露された胎児では、先天異常、特に心血管系で異常が発生するリスクが高くなることが示されている。

妊娠中は、胎児へのリスクを考慮してもなお本剤の使用が正当とみなされる場合にのみ使用すべきである。

FDA: Pregnancy Category - D

Usage in Pregnancy: *Teratogenic Effects:* Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations… **this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.** **Paxil product label 2005**

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人生のあらゆるステージを通じて:

SSRIは女性の健康に貢献しているのです

Across The Life Cycle: SSRIs In Women's Health

GSK Speakers Bureau Slides

Mary Beth

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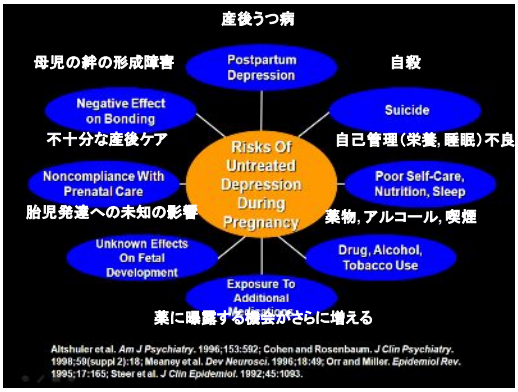
妊娠期の 'うつ' を治療しない場合の危険性



Altshuler et al. *Am J Psychiatry*. 1996;153:592; Cohen and Rosenbaum. *J Clin Psychiatry*. 1998;59(suppl 2):18; Meaney et al. *Dev Neurosci*. 1996;18:49; Orr and Miller. *Epidemiol Rev*. 1995;17:165; Steer et al. *J Clin Epidemiol*. 1992;45:1093.

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妊娠期のSSRI: アウトカム研究の結果

SSRIs In Pregnancy:
Results Of Outcome Studies

胎児障害の
リスク増大なし
No ↑ Risk Of
Poor Fetal
Outcomes

妊娠関連有事象の
リスク増大なし
No ↑ Risk Of
Adverse Pregnancy
Outcome

There are no adequate and well-controlled studies for the use of SSRIs in pregnant women. Medications should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Altshuler et al. *Am J Psychiatry*. 1996;153:592; Brunel et al. *Therapie*. 1994;49:117; Ericson et al. *Eur J Clin Pharmacol*. 1999;55:503; Goldstein et al. *Obstet Gynecol*. 1997;89:713; Kulin et al. *JAMA*. 1998;279:609; McElhatton et al. *Reprod Toxicol*. 1996;10:285; Nulman et al. *N Engl J Med*. 1997;336:258; Pastuszak et al. *JAMA*. 1993;269:2246.

妊娠期のフルオキセチン:
神経発達の評価 New Engl J Med 1997年掲載論文
219人での前向き比較研究結果より

Fluoxetine In Pregnancy:
Neurodevelopment Assessment

	Outcome	Result	
流産	Miscarriage	N/A	データなし
新生児毒性	Neonatal toxicity	No ↑ risk	リスク上昇なし
臓器奇形	Organ malformation	No ↑ risk	リスク上昇なし
発育障害	Growth impairment	No ↑ risk	リスク上昇なし
神経発達	Neurodevelopment	Children followed between 16 months - 7 years of age. No change in IQ scores or language & behavioral development	

There are no adequate and well-controlled st
Medications should be used during pregnanc
to the fetus.

Controlled, prospective study (N=219).
Nulman et al. *N Engl J Med*. 1997;336:258.

16ヶ月から7歳まで追跡した結果、IQ 、言語発達・行動上の発達に影響なし

妊娠期のSSRI: パロキセチン, セルトラリン, フルボキサミン
JAMA 1998年掲載Kulinらの論文
SSRI 222人, 対照235人での多施設コホート研究より

SSRIs In Pregnancy:
Paroxetine, Sertraline, Fluvoxamine

	Outcome	Result	
流産	Miscarriage	No ↑ risk	**リスク上昇なし**
新生児毒性	Neonatal toxicity	N/A	**データなし**
臓器奇形	Organ malformation	No ↑ risk	**リスク上昇なし**
発育障害	Growth impairment	No ↑ risk	**リスク上昇なし**
神経発達	Neurodevelopment	N/A	**データなし**

There are no adequate and well-controlled studies for the use of SSRIs in pregnant women. Medications should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Prospective, controlled, multicenter study (N=222 on SSRI; N=235 on placebo).
Kulin et al. *JAMA*. 1998;279:609.

妊娠期のSSRI: パロキセチン, セルトラリン, フルボキサミン
JAMA 1998年掲載Kulinらの論文
SSRI 222人, 対照235人での多施設コホート研究より

SSRIs In Pregnancy:
Paroxetine, Sertraline, Fluvoxamine

	Outcome	Result	
流産	Miscarriage	No ↑ risk	リスク上昇なし
新生児毒性	Neonatal toxicity	N/A	データなし
臓器奇形	Organ malformation	No ↑ risk	リスク上昇なし
発育障害	Growth impairment	No ↑ risk	リスク上昇なし
神経発達	Neurodevelopment	N/A	データなし

There are no adequate and well-controlled studies for the use of SSRIs in pregnant women. Medications should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Prospective, controlled, multicenter study (N=222 on SSRI; N=235 on placebo).
Kulin et al. *JAMA*. 1998;279:609.

JAMA 1998年掲載Kulinらの論文
短報 新しいSSRI(セルトラリン、パロキセチン、フルボキサミン)を使用した妊婦での妊娠アウトカム 前向き比較多施設共同研究

Brief Report

Pregnancy Outcome Following Maternal Use of the New Selective Serotonin Reuptake Inhibitors
A Prospective Controlled Multicenter Study

Nathalie A. Kulin, MSc; Anna Pastuszak, MSc; Suzanne R. Sage, RN, MS; Betsy Schick-Boschetto, MSN; Glenda Spivey, MS, OT; Marisa Feldkamp, Kelly Ormond, MS; Doreen Matsui, MD; Amy K. Stein-Schechtman, MS; Lola Cook, MS; Joanne Brochu, Michael Reider, MD; Gideon Koren, MD

Context.—Although a large number of women of reproductive age use new selective serotonin reuptake inhibitors (SSRIs) and half of all pregnancies are unplanned, no data exist on the safety of these agents for the human fetus.

Objective.—To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline.

Design.—A prospective, multicenter, controlled cohort study.

Setting.—New Teratology Information Service centers in the United States and Canada.

Patients.—All women who were counseled during pregnancy following exposure to a new SSRI and followed up by the participating centers. Controls were randomly selected from women counseled after exposure to nonteratogenic agents.

Main Outcome Measures.—Rates of major congenital malformations.

Results.—A total of 207 women exposed to an SSRI and 267 controls were studied. Exposure to SSRIs was not associated with either increased risk for major malformations (5/222 live births [4.1%] vs 9/238 live births [3.8%] in the controls; relative risk, 1.06; 95% confidence interval, 0.43-2.62) or higher rates of miscarriage, stillbirth, or prematurity. Mean (SD) birth weights among SSRI users (3439 [505] g) were similar to the controls (3446 [619] g) as were the gestational ages (39.4 [1.7] weeks vs 39.4 [1.6] weeks).

Conclusion.—The new SSRIs, fluvoxamine, paroxetine, and sertraline, do not appear to increase the teratogenic risk when used in their recommended doses.

JAMA. 1998;279:609-610

Patients and Methods

This prospective cohort included all women who contacted 1 of 5 participating Teratology Information Service centers regarding exposure to fluvoxamine, paroxetine, and sertraline during the first trimester of pregnancy for depression. Excluded were women who, in addition to being exposed to a new SSRI, were also exposed to a known human teratogen or drugs of uncertain teratogenicity. The group exposed to SSRIs was matched to

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妊娠期におこる‘うつ’：リスク・ファクター（関連要因）

- ・個人歴または家族歴における‘うつ’の既往
- ・抗うつ剤の突然の中止/一時中断
- ・妊婦に対する支援不足
- ・最近のストレス

Depression During Pregnancy: Risk Factors

- Personal/family history
- Abrupt/preliminary discontinuation of antidepressant
- Poor support
- Recent stressors

Altshuler et al. *J Clin Psychiatry*. 1998;59(suppl 2):29.
Gotlib et al. *J Consult Clin Psychol*. 1989;57:269.

それぞれの利点　半減期が短い薬剤 vs 長い薬剤

・短い薬剤	・長い薬剤
–副作用の消失が早い	–副作用の消失が遅い
–効果の消失も早く、コントロールしやすい	–効果が消失するまでの時間が長い
–薬で起こった症状かどうかが、患者自身にわかりやすい	–薬で起こった症状かどうかが、患者自身にわかりにくい

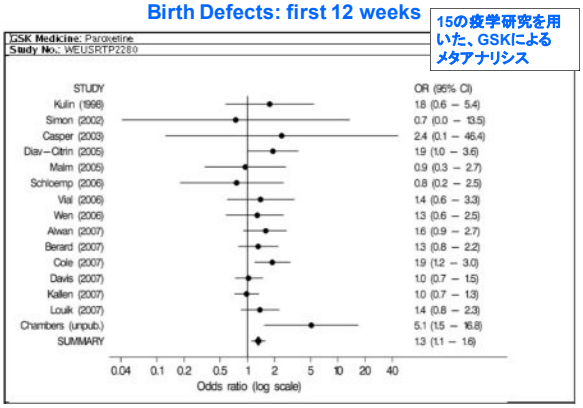
Advantages Of Short Versus Long Half-life

Short half-life	Long half-life
– shorter time to resolution of side effects	– longer time to resolution of side effects
– more rapid, controlled washout	– longer washout
– patients' recognition of symptoms with drug	– patients unlikely to associate symptoms with drug

パキシルによる先天異常：妊娠初期12週間内服

Birth Defects: first 12 weeks

15の疫学研究を用いた、GSKによるメタアナリシス

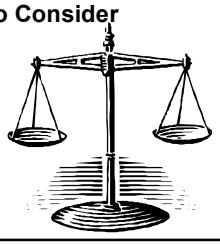


妊娠中の抗うつ剤：考慮すべき危険性

- ・子宮内胎児死亡
- ・周産期の障害
- ・催奇形性
- ・発育障害
- ・神経行動学的後遺症

Antidepressants In Pregnancy: Risks To Consider

- Intrauterine death
- Perinatal difficulties
- Teratogenicity
- Growth Impairment
- Neurobehavioral sequelae



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STI Psychopharmacology BULLETIN

精神薬理学雑誌　2003年春　37巻 増刊号

71

Archives of Pediatrics & Adolescent Medicine 2004;　158(4): 307-8.

論説
妊娠後期における抗うつ剤使用後の離脱（退薬）症状

EDITORIAL

Discontinuation Syndrome Following Late Pregnancy Exposure to Antidepressan

Gideon Koren, MD, FABMT, FRCPC
Division of Clinical Pharmacology and Toxicology
The Hospital for Sick Children
555 University Ave
Toronto, Ontario
Canada M5G1X8
(e-mail: gkoren@sickkids.ca)

DEPRESSION MAY AFFECT UP TO 20% OF pregnant women,[1,2] which translates into 80000 women in the United States per year. There is increasing evidence to suggest adverse effects of untreated depression during pregnancy, including increased risk of miscarriage, prematurity, growth retardation, and low Apgar scores.[3-5] Importantly, untreated or even undertreated depression can cause increased maternal risk of poor prenatal care, suicidal ideation, suicide attempts, and postpartum depression.[5,6]

A second issue in late pregnancy use of antidepressants and resultant neonatal discontinuation, or withdrawal, syndrome, characterized by poor neonatal adaptation and other symptoms similar to those seen in adults. When a drug is discontinued abruptly, infants can experience perinatal complications. In 2002, Costei et al[10] reported characteristics of this syndrome in a prospective cohort of neonates exposed to paroxetine in late pregnancy.

In this issue of the ARCHIVES, Källén[22] reports on the findings of a population-based Swedish registry examining late-pregnancy exposure to antidepressants and iden-

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妊娠中のパロキセチン使用と先天性心血管系異常に関するリスク評価

2008年6月

Article

Evaluation of the Risk of Congenital Cardiovascular Defects Associated With Use of Paroxetine During Pregnancy

Adrienne Einarson, R.N.
Alessandra Pistelli, M.D., Ph.D.
Marco DeSantis, M.D.
Heli Malm, M.D.
Wolfgang D. Paulus, M.D.
Alice Panchaud, Ph.D.
Debra Kennedy, M.D.
Thomas R. Einarson, Ph.D.
Gideon Koren, M.D.

Objective: In 2005–2006, several studies noted an increased risk of cardiovascular birth defects associated with maternal use of paroxetine compared with other antidepressants in the same class. In this study, the authors sought to determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.

Method: From teratology information services around the world, the authors collected prospectively ascertained, unpublished cases of infants exposed to paroxetine early in the first trimester of pregnancy and compared them with an unexposed cohort. The authors also contacted the authors of published database studies on antidepressants as a class to determine how many of the women in those studies had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Results: The authors were able to ascertain the outcomes of 1,174 infants from eight services. The rates of cardiac defects in the prospective [illegible] exposed group [illegible] the database [illegible] four studies [illegible]

Conclusion: [illegible] appear to be [illegible] risk of cardiac [illegible] use in early [illegible] in more than [illegible] within the [illegible] proximately [illegible]

(Am J Psychiatry 2008; 165:749–752)

結論：妊娠早期におけるパロキセチン使用による児の心血管系異常増加は関連は認められず、異常発生率は一般集団と同じ約1%であった。

前ページ Einarson論文へのLetter（コメント）

2008年11月

妊娠期の‘うつ’にパロキセチンを使うべきか？

「パロキセチンの妊娠期の使用については、まだ安全性も有効性も確立していないとすべきである。」

Letters to the Editor

Should Paroxetine Be Used to Treat Depression During Pregnancy?

To the Editor: In the June 2008 issue of the *Journal*, Adrienne Einarson, R.N. et al. (1) concluded that the existing evidence does not suggest an association between the use of paroxetine during pregnancy and congenital cardiovascular defects. Their conclusion was based on an observational study and five previous cohort studies. The authors stressed the need to treat depression during pregnancy and stated that if appropriate treatment includes paroxetine, the findings of their study "should reassure women and their health care providers" (1, p. 752). This endorsement is at odds with regulatory warnings (2).

The design and reporting of the study raise questions pertaining to claimed results. No data are provided regarding 1) baseline characteristics of exposed women and unexposed comparison women, 2) whether the analysis is intention-to-treat or per protocol, 3) loss to follow-up, or 4) proportion with evaluable outcomes. Both the exposure levels and procedures to select comparison women were unclear. Additionally, the outcome assessment was not blinded to exposure, and treatment for ambiguous diagnoses was unclear.

Einarson et al. included a secondary analysis of five cohort studies of paroxetine exposure during pregnancy. Although four of these studies included comparison groups and two required [illegible]

risk of congenital cardiovascular defects associated with the use of paroxetine in pregnancy. Am J Psychiatry 2008; 165:749–752
2. US Food and Drug Administration: FDA Advising of Risk of Birth Defects With Paxil. P05-97. Rockville, Md, FDA News, 2005. http://www.fda.gov/bbs/topics/NEWS/2005/NEW01270.html
3. Kallen BA, Olausson P: Maternal use of selective serotonin reuptake inhibitors in early pregnancy and infant congenital malformations. Birth Defects Res A Clin Mol Teratol 2007; 79:301–308.
4. GlaxoSmithKline: Epidemiology Study: Paroxetine in the First Trimester and the Prevalence of Congenital Malformations. EPI40404. http://ctr.gsk.co.uk/Summary/paroxetine/studylist.asp
5. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN: Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 295:499–507.

BARBARA MINTZES, Ph.D.
Vancouver, British Columbia
JON JUREIDINI, M.B.B.S., F.R.A.N.Z.C.P., Ph.D.
Adelaide, South Australia

This letter (doi: 10.1176/appi.ajp.2008.08040573) was accepted for publication in August 2008.

The authors report no competing interests.

Einarson論文の後日談

雑誌編集者が、2008年8月 Einarson論文へのLetter（コメント）を受領

This letter (doi: 10.1176/appi.ajp.2008.08040573r) was accepted for publication in August 2008.

雑誌編集者は、2008年9月 Einarson論文について以下の訂正記事を掲載

Errors in the Journal's *editorial office resulted in the [illegible] sures of Ms. Einarson and her co-authors not accompanying the original article and so they are presented here: Dr. [illegible] and Ms. Einarson have received research support from [illegible] sen-Ortho and Wyeth. Dr. Koren has received research support from Apotex, Duchesnay, Novartis, and Pfizer. Ms. Einarson has received unrestricted research grants from GlaxoSmithKline for studying ondansetron in pregnancy and from [illegible] non for studying mirtazapine in pregnancy. Dr. Einarson has received research support from Bristol-Myers Squibb, Janssen-Ortho, Lundbeck, Novo Nordisk, and Organon. The remaining authors report no competing interests.*

オリジナル論文では、Einarsonと共著者の利益相反が開示されていなかったので、ここに開示する。（中略）

・・・Dr. Korenはアボテックス、デュシェネ、ノバルティス、ファイザーから研究サポートを受けた。Ms. EinarsonはGSKから研究費の提供を受け妊娠中のオンダンセトロンに関する研究を実施、Dr. Einarsonはブリストル・マイヤーズ・スクイブ、イーライリリー、ヤンセン・オルソ、ルンドベック、ノボノルディスク、オルガノンから研究のサポートを受けていた。・・・

そして、

2008年11月 Einarson論文へのLetter（コメント）掲載

Einarson論文の最終著者Gideon Korenから GSK担当者へのE-mail

2006年11月14日 「パロキセチンのメタアナリシスについて」
拝啓サラ様
お分かりと思いますが、あなた以外のGSK研究者の連絡先を知りませんので、あなたにご連絡します。こちらとしては、求められた法的手続きには応じましたが、そちらからはいまだに対応していただいておりません。データ共有がこのように遅れているのが、そちらの無関心によるものか、非効率な手続きによるものかは知りません。いずれにしてもデータを迅速にお送りいただけない場合は、我々で解析を進め、論文には、GSKからはデータ提供を受けられなかったと書くことになりますよ。 Gideon Koren

"Gideon Koren" <[Redacted]>
14-Nov-2006 14:19
To: sara.a.ephross@gsk.com, "david carpenter" <david.j.carpenter@gsk.com>
cc: "Thomas Einarson" <teinarson@utoronto.ca>, "Bar Oz" <bar-oz@md.huji.ac.il>
Subject: Re: Fw: Meta analysis of paroxetine

Dear Sara, as you must know, I cannot approach the different GSK researchers as I do not know who they are and their contacts. I want to remind you that our initiative was in response to request BY your legal experts, yet, it feels as if we cannot get much. I do not know if this reflects reluctance to share data, indefference, or just a very inefficient system. Unless we get from you data promptly, we will go ahead with our analysis and mention in the manuscript that attempts to receive data from GSK have failed. GK

胎児期を通して三環系抗うつ剤またはフルオキセチンに曝された児の発育：前向き比較研究

Article

Child Development Following Exposure to Tricyclic Antidepressants or Fluoxetine Throughout Fetal Life: A Prospective, Controlled Study

Irena Nulman, M.D.
Joanne Rovet, Ph.D.
Donna E. Stewart, M.D.
Jacob Wolpin, Ph.D.
Pia Pace-Asciak, B.A.
Samar Shuhaiber, M.Sc.
Gideon Koren, M.D.

Objective: Previous work suggested that first-trimester exposure to tricyclic antidepressants or fluoxetine does not affect adversely child IQ and language development. However, many women need antidepressant throughout pregnancy to avoid morbidity and suicide attempts. Little is known about the fetal safety of tricyclic antidepressants and fluoxetine when taken throughout pregnancy. The goal of this study was to assess the effects of tricyclic antidepressants and fluoxetine used throughout gestation on child IQ, language, and behavior.

Method: In a prospective study, mothers exposed throughout gestation to tricyclic antidepressants or fluoxetine (N=40) and an unexposed, not [illegible] comparison group (N=40) were interviewed. The three groups were [illegible] in terms of the children's IQ, [illegible] behavior, and temperament [illegible] ages 15 and 21 months. The [illegible] worked for independent variables [illegible] duration and severity of maternal [illegible] on duration of pharmacological treatment, number of depression episodes after delivery, maternal IQ, socioeconomic status, cigarette smoking, and alcohol use.

Results: Neither tricyclic antidepressants nor fluoxetine adversely affected the child's global IQ, language development, or behavior. IQ was significantly and negatively associated with duration of depression, whereas language was negatively associated with number of depression episodes after delivery.

Conclusions: Exposure to tricyclic antidepressants or fluoxetine throughout gestation does not appear to adversely affect cognition, language development, or the temperament of preschool and early-school children. In contrast, mothers' depression is associated with less cognitive and language achievement by their children. When needed, adequate antidepressant therapy should be instituted and maintained during pregnancy and postpartum.

(Am J Psychiatry 2002; 159:1889–1895)

結論：胎児期の三環系抗うつ剤またはフルオキセチン曝露は、幼稚園や小学生低学年での認知・言語発達、気質に対する悪影響はなかった。

しかし、母親のうつは、子供の認知・言語発達の抑制と関連していた。妊娠期と産後の適切なうつ治療が必要である。

G Koren 2007
女性は、薬による催奇形性をどのように認識しているか
Can J Clin Pharmacology 14, e10-e16

G Koren 2007
The Way Women Perceive Teratogenic Risk
Can J Clin Pharmacology 14, e10-e16

マザーリスク・プログラム HP:
カナダ トロント小児病院で1985年から開始された妊娠中の薬の安全性に関する情報収集と提供のシステム

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SheKnows.com HP

妊娠＆抗うつ剤
・・・多くの女性が抗うつ剤による先天障害を恐れているが、最近の研究結果では、妊娠期の抗うつ剤は安全という報告もある。

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SheKnows.com HP

妊娠とうつについて

新しい研究によると、抗うつ剤は安全

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BMJ **英国医師会雑誌2009年掲載論文RESEARCH**
「妊娠中のSSRIと先天異常: 大規模コホート研究」

Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study

結果よりResults:

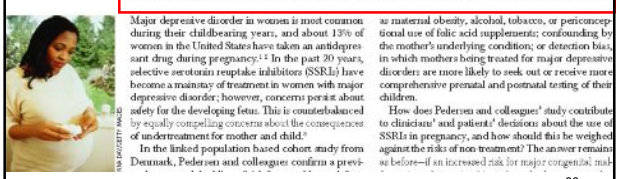
妊娠中のSSRIと出生児の心房/心室中隔欠損
SSRI in pregnancy and septal heart defects

SSRIなし 0.5%
unexposed children

SSRI服用 0.9%
children whose mothers were prescribed any SSRI

2種類以上SSRI服用 2.1%
children whose mother were prescribed more than one type of SSRI

前ページの英国医師会雑誌2009年掲載論文
「妊娠中のSSRIと先天異常: 大規模コホート研究」
を取り上げた論説記事



（薬による）害のリスクはわずかでも、最適に近い治療や無治療でのリスクとのバランスを考える必要がある。

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米国精神医学会

米国産科婦人科学会

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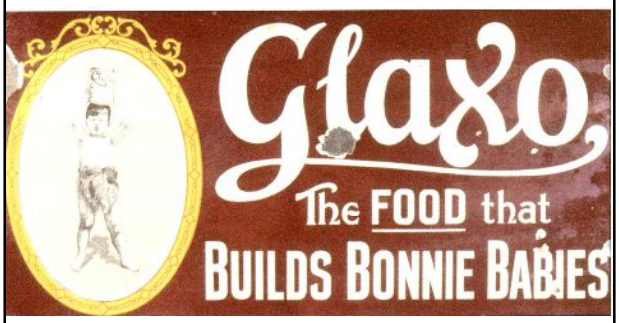
TIME誌　2010年2月11日記事
産後のうつ: 妊娠中からのシグナル
Postpartum Depression: Signaled During Pregnancy ? より

毎年米国で出産する女性の14～23%が、妊娠中の‘うつ’を経験している（米国産科婦人科学会と米国精神医学会による2009年の合同報告）。2010年1月21日、米国産科婦人科学会は緊急声明を発表し、妊娠中のなるべく早い時期に‘うつ’のスクリーニングが必要とした。学会メンバーに対して「研究により、母親の‘うつ’を治療せずにおいた場合、新生児の認知機能、神経機能や運動機能の発達に悪い影響を及ぼすことが示された」と伝えている。文書では、産科医によるルチーンの診察で‘うつ’のスクリーニングをすることを強く勧めている。

From 14% to 23% of women giving birth in the U.S. each year experience a depressive disorder during pregnancy, according to a joint report published in September 2009 by the American College of Obstetricians and Gynecologists (ACOG) and the American Psychiatric Association. On Jan. 21, the ACOG made an urgent call for depression screening as early as possible during pregnancy. "Studies have shown that untreated maternal depression negatively affects an infant's cognitive, neurologic and motor skill development," read an ACOG communiqué issued to its members. The document went on to "strongly encourage" obstetricians to screen patients for depression as part of their routine practice.

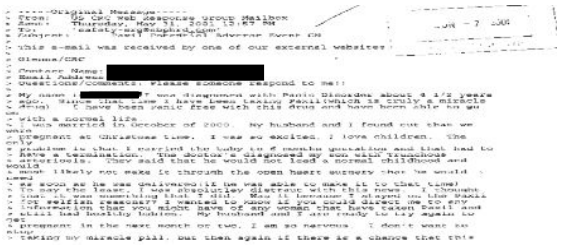
Time Magazine 2010

グラクソによる粉ミルクの広告
「健康な赤ちゃんを育てる食品」



2001年5月31日「パキシルの有害事象について」患者からの問い合わせメイル

私は、4年半ほど前にパニック障害と診断されました。それ以来パキシル（まさに魔法の薬です）をのんでいます。この薬でパニックはなくなり、普通の生活を送ることができています。2000年10月には結婚しました。クリスマスには妊娠がわかりました。子供は大好きで、とても嬉しかったです。でも妊娠6ヶ月のときに、息子は総動脈幹症であることがわかり、子供を下ろさざるを得ませんでした。医師によると、生まれてすぐ開胸手術が必要で、もし助かったとしても普通の子供時代は送れないと言われたからです。私は我を失いました。私に原因があるのだろうか、自分のためにパキシルをのんだことが原因なんだろうかと考えました。パキシルをのんで健康な子供を産んだ女性のことをご存知でしたら教えていただけないでしょうか。私たち夫婦はもう一度子供を作りたいと思っています。パキシルを止めたくはありませんが、また同じことが、と思うと・・・。



SR	ABBREV_DESCR		SHORT_DESCR
IN	Unrelated	関連なし	Unrelated
IN	Unlikely	ほとんど関連なし	Unlikely
IN	Possible	関連あるかもしれない	Possible
IN	Probable	おそらく関連あり	Probable
IN	Almost certain	ほぼ関連あり	Almost certain
IN	No	なし	No
IN	Unknown	不明	Unknown
IN	Not Assessable	評価不能	Not Assessable

私は、4年半ほど前にパニック障害と診断されました。それ以来パキシル（まさに魔法の薬です）をのんでいます。この薬でパニックはなくなり、普通の生活を送ることができています。2000年10月には結婚しました。クリスマスには妊娠がわかりました。子供は大好きで、とても嬉しかったです。**でも妊娠6ヶ月のときに、息子は総動脈幹症であることがわかり、子供を下ろさざるを得ませんでした。医師によると、生まれてすぐ開胸手術が必要で、もし助かったとしても普通の子供時代は送れないと言われたからです。私は我を失いました。私に原因があるのだろうか、自分のためにパキシルをのんだことが原因なんだろうかと考えました。**

My name is*** I was diagnosed with Panic Disorder about 4.5 years ago. Since this time I have been taking Paxil (which is truly a miracle drug). I have been panic free with this drug and have been able to go on with a normal life. I was married in October of 2000. My husband and I found out that we were pregnant at Christmas time. I as so excited, I love children.

The only problem is that **I carried the baby to 6 months gestation and that had to have a termination. The doctors diagnosed my son with Truncus arteriosus. They said he would not lead a normal life and most likely would not lead a normal childhood** and most likely would not make it through the open heart surgery he would need …

I was absolutely distraught with this news…I thought it was something I did. Was it because I stayed on Paxil for selfish reasons.

パキシルをのんで健康な子供を産んだ女性のことをご存知でしたら教えていただけないでしょうか。私たち夫婦は来月かその後に、もう一度子供を作りたいと思っています。パキシルを止めたくはありませんが、**また同じことが起こるのならば、当分の間パキシルを止めようと思います。**できるだけ早くご返事ください。パキシルには満足していますし、この薬を製造してくれる御社には感謝しています。とにかく普通の生活を続けて、子供を持ちたいのです。なるべく早くご連絡くださるようお願いします。

I wanted to know if you can direct me to any information on women who have taken Paxil and still had healthy babies. My husband and I are ready to get pregnant again in the next month or two and I am so nervous. I don't want to stop taking my miracle pill but **if there is a chance that this might hurt of affect the baby I want to know upfront and I will somehow stop taking it for the timebeing**. Please contact me as soon as possible. I love everything that this drug has done for me and I am so thankful that your company had this available for me. I just want to continue to have a normal life, and have the child that I have always wanted. Please contact me as soon as possible.

前ページの英国医師会雑誌2009年掲載論文
「妊娠中のSSRIと先天異常: 大規模コホート研究」
を取り上げた論説記事

Editorials represent the opinions of the authors and not necessarily those of the *BMJ* or BMA

EDITORIALS

女性の大うつ病は妊娠期にもっとも一般的であり、米国では約13%の妊婦が抗うつ剤をのんでいる。

Selective serotonin reuptake inhibitors and congenital malformations

The small risk of harm must be balanced against risk of suboptimal or no treatment

Major depressive disorder in women is most common during their childbearing years, and about 13% of women in the United States have taken an antidepressant drug during pregnancy.[1,2] In the past 20 years, selective serotonin reuptake inhibitors (SSRIs) have become a mainstay of treatment in women with major depressive disorder; however, concerns persist about safety for the developing fetus. This is counterbalanced by equally compelling concerns about the consequences of undertreatment for mother and child.[3]

In the linked population based cohort study from Denmark, Pedersen and colleagues confirm a previ-

as maternal obesity, alcohol, tobacco, or periconceptional use of folic acid supplements; confounding by the mother's underlying condition; or detection bias, in which mothers being treated for major depressive disorders are more likely to seek out or receive more comprehensive prenatal and postnatal testing of their children.

How does Pedersen and colleagues' study contribute to clinicians' and patients' decisions about the use of SSRIs in pregnancy, and how should this be weighed against the risks of non-treatment? The answer remains as before—if an increased risk for major congenital mal-

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大うつ病と抗うつ剤療法:
妊娠と新生児に対する影響の大きさ

Article

Major Depression and Antidepressant Treatment: Impact on Pregnancy and Neonatal Outcomes

Katherine L. Wisner, M.D.
Dorothy K.Y. Sit, M.D.
Barbara H. Hanusa, Ph.D.
Eydie L. Moses Kolko, M.D.
Debra L. Bogen, M.D.
Diane F. Hunker, R.N.
James M. Perel, Ph.D.
Sonya Jones-Ivy, M.D.

Objective: Selective serotonin reuptake inhibitor (SSRI) use during pregnancy incurs slow absolute risk for major malformations; however, other adverse outcomes have been reported. Major depression also affects reproductive outcomes. This study examined whether 1) minor physical anomalies, 2) maternal weight gain and infant birth weight, 3) preterm birth, and 4) neonatal adaptation are affected by SSRI or depression exposure.

Method: This prospective observational investigation included maternal assessments at 20-, 30-, and 36-weeks of gestation. Neonatal outcomes were obtained by blinded review of delivery records and infant examinations. Pregnant women (N=228) were categorized into three mutually exclusive exposure groups: 1) no SSRI, no depression (N=131); 2) SSRI exposure (N=71), either continuous (N=48) or partial (N=23); and 3) major depressive disorder (N=30), either continuous (N=16) or partial (N=22). The mean depressive symptom level of the group with continuous depression and no SSRI exposure was significantly greater than for all other groups, demonstrating the expected treatment effect of SSRIs. Main outcomes were minor physical anomalies, maternal weight gain, infant birth weight, pregnancy duration, and neonatal characteristics.

Results: Infants exposed to either SSRIs or depression continuously across gestation were more likely to be born preterm than infants with partial or no exposure. Neither SSRI nor depression exposure increased risk for minor physical anomalies or reduced maternal weight gain. Mean infant birth weights were equivalent. Other neonatal outcomes were similar, except 5-minute Apgar scores.

Conclusions: For depressed pregnant women, both continuous SSRI exposure and continuous untreated depression were associated with preterm birth rates exceeding 25%.

Am J Psychiatry 2009; 166:557-566

結論: 大うつ病の女性は、SSRIで治療した場合と治療しなかった場合どちらも、うつ病でない女性に比べ早産率が20%高かった。

英国医師会雑誌BMJ 2009年11月14日 p1106
World NEWS: 米国での比較的高い新生児死亡率の原因は早産の多さである。

2005年における米国での出産のうち12.4%が早産である。一方、アイルランドは5.5%、フランス6.3%、イングランドとウェールズ7.5%である。

米国での高新生児死亡率の原因は、早産の多さによっている。

NEWS

Relatively high infant mortality in the US is largely due to

Janice Hopkins Tanne
NEW YORK

The United States ranks 30th in the world in terms of infant mortality, behind most European countries and Canada, Australia, New Zealand, Hong Kong, Singapore, Japan, and Israel, says a report from the US Centers for Disease Control and Prevention (www.cdc.gov/nchs/data/databriefs/db23.htm).

Singaporehad the world's lowest infant mortality rate, at 2.1 deaths per 1000 live births, at the date, from 2004 and 2005. The US has slipped over the past half century, the report says. "The United States' international

ranking in infant mortality fell from 14th in the world in 1960, to 23rd in 1990, to 29th in 2004, and 30th in 2005.

"In 2005, 22 countries had infant mortality rates of 5.0 infant deaths per 1000 live births or lower. The lowest infant mortality rates (3.0 or lower) were found in selected Scandinavian (Sweden and Finland) and East Asian (Japan, Hong Kong, and Singapore) countries. The rate in the United States was 6.86 in 2005."

Much of the high infant mortality in the US is because of the high percentage of preterm births in the US in comparison

In the US 12.4% of live births in 2005 were preterm, compared with 5.5% in Ireland, 6.3% in France, and 7.5% in England and Wales, the report from the CDC found

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診察室や病室のプライバシーの中で，患者が医師に信頼を寄せ，その意見を求める。この交流こそが，すべての医師の原点である。

"The occasion when in the intimacy of the consulting room or sick room, a person seeks the advice of a doctor, whom she trusts. This is a consultation and all else in the practice of medicine derives from it."

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James Spence: The Consultation

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心の健康をとるか、健全な赤ちゃんをとるかは難しい選択です。しかし、この薬が問題を引き起こすことがわかっていれば、‘うつ’に対処する別の方法を考えると思います。

BEAUTY HEALTH & FITNESS, pregnancy and antidepressants

"It's difficult because you need good mental health and a healthy baby. But if I had known this drug could cause problems, I would have found another way to deal with my depression"

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