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Research article

Drug therapy and adverse drug reactions to terbutaline in obstetric patients: a prospective cohort study in hospitalized women

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Abstract

Background: Adverse drug reactions (ADR's) could be expected more frequently in pregnant women. This study was performed in order to identify ADR's to tocolytic drugs in hospitalised pregnant women.

Methods: A prospective cohort study was performed in two General Hospitals of the *Instituto Mexicano del Seguro Social* (IMSS) in Mexico City. Two hundred and seven women undergoing labor, premature labor, threatened abortion or suffering any obstetric related disease were included. Drug prescription and signs and symptoms of any potential ADR were registered daily during the hospital stay. Any potential ADR to tocolytic drugs was evaluated and classified by three of the authors using the Kramer's algorithm.

Results: Of the 207 patients, an ADR was positively classified in 25 cases (12.1%, CI95% 8.1 to 17.5%). All ADR's were classified as minor reactions. Grouping patients with diagnosis of threatened abortion, premature labor or under labor (n= 114), 24 ADR's were related to terbutaline, accounting for a rate of 21.1 ADR's per 100 obstetric patients. Obstetric patients suffering an ADR were older than obstetric patients without any ADR. However, the former received less drugs/day $\times$ patient^{-1} and had a shorter hospital stay ($p < 0.05$) whereas the dose of terbutaline was similar between the two groups. Terbutaline inhibited uterine motility in women with and without any ADR at a similar rate, 70 and 76% respectively ($x^2 = 0.07$; $p = 0.8$).

Conclusion: Terbutaline, used as a tocolytic drug, was related to a high frequency of minor ADRs and to a high rate of effcicacy.

Background

The ADR's are considered as a major public health problem [1]. Being the fourth cause of general deaths [2], the ADR's are costly and represent a significant rate of hospital admissions [3,4]. Furthermore, the number of drugs available for prescription in the clinical setting is increasing every day. It is therefore important to acquire, interpret and report all ADR's identified with any drug [2]. Furthermore, pharmacovigilance in special populations, e.g. pregnancy women, could be useful to identify unexpected responses probably expressing unusual pharmacokinetic profiles as a result of their particular physiological state [5,6].

Multiple methods have been used for pharmacovigilance, and despite spontaneous reporting is the simplest one, it has been of low efficacy in Mexican medical practice [7]. Furthermore, in Latin-America only a limited number of drug utilization studies done in order to report any ADR during clinical practice are available. In Mexico, the population is growing at a yearly rate of 1.85, representing approximately more than 2 millions of newborns every year [8]. The IMSS, one of the two social health systems available in Mexico, is responsible to attend approximately 60% of the Mexican citizens and also a considerable rate of deliveries [9], resulting into a major source of information on drugs utilization. The present study was performed in order to identify any ADR to tocolytic drugs in a prospective cohort of hospitalised pregnant women requiring medical attention at the IMSS.

Materials and Methods

After approval by the National Research Committee of the IMSS, the study was performed at the Gynecology and Obstetric units of two secondary-care general hospitals. Selection of these hospitals was based on their similar characteristics of medical care while they had a different geographic distribution, one at the north and other at the south of Mexico City. A minimal sample size of 148 patients was estimated using previous studies on ADR's with an expected frequency of ≥ 2.5% and a significant level of 5% [10,11]. During the study period, 207 women in labor, premature labor, threatened abortion or suffering any obstetrical related disease referred to any of the two hospitals over a 4-month period were included into the cohort, and data were obtained during their hospital stay.

Data collection

General information including age (yr.), level of education (according to the basic Mexican scholar system, patients were grouped into ≤ 6 and >6 years of scholar level), diagnosis (cesarean section, labor, premature labor, threatened abortion, or post-cesarean complications), and hospital stay (days) were obtained. Drugs and dose administrated were obtained from the medical and nursery records. Patients were questioned daily, in relation to the presence or not, of symptoms relating to drug administration. Nurses trained for purpose of the study collected data and an Obstetrician confirmed clinical information.

Causality assessment

For identifying any ADR, the Kramer's algorithm was used [12–14]. This system was previously translated into Spanish and successfully used in pediatric patients [15]. Briefly, the algorithm contains 56 questions grouped in six decision-making axes, and it evaluates previous experiences with any drug, potential etiologies of the ADR, a temporary relationship between drug administration and the presence of the ADR, the possibility of an overdoses, and any re-challenge with the suspected drug. Each axe is graded and a total score is obtained to classify the reaction as improbable (<0), possible (0,+1,+2,+3), probable (+4,+5) and definitive (+6,+7). For patients receiving more than one drug, each drug was evaluated by means of the algorithm. Any possibility of drugs interaction was evaluated by means of the Drug interaction program (The Medical Letter, Inc., New Rochelle, NY, USA). An ADR was positively qualified if two or all the evaluators qualified a suspected ADR as either probable or definitive. The file of each patient was reviewed independently by three of the authors trained to use the algorithm (AA Nava-Ocampo, JA Palma-Aguirre and H Sumano-López). Inter-observer agreement among the three evaluators in relation to the scores given to every potential ADR was computed by means of a Kappa analysis at a $p < 0.05$ level [16,17]. Finally, severity of each ADR was scored according to Capellá and Laporte into mortal, severe (any life-threatening reaction), moderate (any reaction requiring hospitalization or requiring urgent atention), or mild [18].

Statistical analysis

Data from all patients were summarized by using descriptive statistics. Patients were further goruped into patients suffering or not any ADR. Except for vitamins, all drugs received by patients were presented as only one active principle. We therefore counted all drugs daily received by each patient and obtained a mean value. Results were then summarized and a final mean value and SD of number of drugs/day × patient^{-1} was obtained. The unpaired Student t test was used to compare age and drugs/day × patient^{-1} between patients suffering or not an ADR. The dose of terbutaline was also compared between the two groups by means of the unpaired Student t test. The Fishers' exact chi-square test was used to evaluate differences in diagnosis and type of drug used for uterine activity inhibition (terbutaline, indometacine, or none) between groups. The significant level for all statistical analyses was fixed at a $p < 0.05$. When used, the parametric 95% confidence interval for the difference was computed.

Software

Data were collected in a predesigned Microsoft® Excel 97 form. For statistical anaylsis, we used the Epi-Info® 6 v. 6.04d (The Center for Disease Control and Prevention, Atlanta, Georgia, USA).

Results

Demographic data were summarized in Table 1. Patients were young people, most of them have the basic education level, and patients undergoing cesarean section was the the major clinical condition.

Table 1: Characteristics of the population

	n = 207
AGE (years)*	27.2 ± 5.2
SCOLARITY	
≤ 6 yr	36(17.4)
>6 yr	171 (82.6)
DIAGNOSTICS	
Threatened abortion	27(13.1)
Premature labor	48 (23.2)
Labor	39(18.8)
Cesarean section	75 (36.2)
Post-cesarean complications	18(8.7)
HOSPITAL STAY (days)*	3.1 ± 0.7

* data expressed as mean ± sd

In relation to the ADR's, agreeement among the reviewers for classification of each ADR was satisfactory (Kappa > 0.92). Of the 207 patients included in the cohort, 28 presented any suspected ADR, being 25 positively classified (12.1%, 95%CI 8.1 to 17.5%). Grouping patients with diagnosis of threatened abortion, premature labor or under labor (n= 114), 24 ADR's were related to terbutaline, accounting for a rate of 21.1 ADR's per 100 obstetric patients.

Patients suffering an ADR were slightly but significantly older than those wihout any ADR (Table 2). They also were attended mainly for premature labor, have a lower hospital stay, and they were mainly receiving terbutaline. However, the dose of terbutaline was similar between the two groups. The tocolytic therapy with terbutaline inhibited uterine motility in women with with and without any ADR in a similar rate, 70 and 76% (x^2 0.07; p = 0.8), respectively. Of the 24 patients suffering an ADR to terbutaline, tremor was present in all patients, dizziness in seven, confusion in six, depression in five, adynamia in three, astenia in other three and headache also in three patients, and loss of equilibrium in one, irritability in one, and palpitations and aggressiveness in another patient. The only patient suffering an ADR to indomethacin referred abdominal discomform. All ADR's were classified as minor reactions, and according with the obstetricians did not merit to prolong the hospital stay, any additional treatment or drug discontinuation, and no fetal complications was reported by the patient or at the maternal records during the hospital stay.

Table 2: Characteristics of patients with diagnosis of threatened abortion, premature labor or labor in relation to the presence or not of any ADR.

	With ADR (n = 25)	Without ADR (n = 89)	Significant level
Age (yr., mean ± SD)	28.8 ± 5.9	25.6 ± 6.0	p = 0.02
DIAGNOSIS			
Threatened abortion	4(16%)	23 (25.8%)	
Premature labor	20 (80%)	28(31.5%)	<0.001
Labor	1 (4%)	38 (42.7%)	
HOSPITAL STAY (days)			
≤ 3	20 (80%)	45 (50.6%)	p= 0.016
>3	5 (20%)	44 (49.4%)	
DRUGS/DAY × PATIENT^{-1}			
Mean ± SD	3.3 ± 1.3	4.4 ± 2.2	p = 0.02
UTERINE INHIBITOR			
a) Terbutaline	24 (96%)	19(21.3%)	
b) Indomethacin	1 (4%)	35 (40.4%)	p < 0.001
c) None	-	34 (38.3%)	
TERBUTALINE DOSE (mg/day)			
Mean ± SD	13.0 ± 3.5	14.5 ± 2.2	p > 0.05
Range	5–15	5–15	

Discussion

Kramer et al., created an algorithm to identify and qualify any ADR without any drug assay [12–14]. However, some problems have emerged with its use. It needs to be translated and adapted for using in different countries, as it happened to us. The algorithm is extensive, and therefore time-consuming. It requires multiple specific information that was collected due to the prospective nature of the present study. Some data, however, could not be available in the clinical file for a retrospective evaluation.

Despite the Council of the International Organization of Medical Sciences has provided definitions and basic requirements for the proper use of ADR terminology [19], a diagnosis is often difficult to establish due to the presence of clinical conditions or prescription of two or more drugs. Casuality assessment for ADR's is therefore often difficult in the clinical setting [20]. Comparisons among the reported ADR's frequencies are also problematic due to the differences observed among the studies, including the population (e.g. pediatric, adults or old patients), gender, set of the study (e.g. emergency rooms or hospitalized patients), and method of measurement (e.g. therapeutic drug monitoring, spontaneous reports) [4,10,11,21–28] . The frequency of 12.1% of ADR's reported in the current study was lower than the 33.3% reported for all admissions at an Indian hospital [29], and than 28.2% reported at a Universitary hospital [11]. However, it resulted higher than 2.4 to 3.7% of ADR's observed in other studies for hospitalized patients [4,10]. Differences could be explained by the fact that obstetric patients do receive a lesser amount or less agressive theraphy than patients attended e.g. at internal medical wards.

We studied women patients requiring hospital attention for non-accidental causes, and despite a high incidence of ADR's was identified in patients receiving terbutaline for premature labor and threatened abortion, mortality was not present. Terbutaline is worldwide formerly approved for the treatment of asthma. As it was recently reviewed by Lam et al. [30], in the United States the off-label utility of terbutaline as a tocolytic agent has been known by clinicians for more than 20 years, estimating that at least 260,000 women are yearly receiving terbutaline during pregnancy, being the most popular prescribed β-mimetic for tocolysis in the USA. In Mexico, it is also extensively used in the obstetric wards provably favored by the fact that other therapuetic options as ritodrine did never arrive to our country. In fact, ritodrine was removed from the marked in the United States [30].

Terbutaline is clearly an effective inhibitor of uterine activity [31,32], and its ADR's are abated with discontinuing treatment only. In our study, no differences in dose of terbutaline were detected between patients suffering or not an ADR. Although efficacy was not our goal, the uterine inhibitor effects of terbutaline resulted in a high rate of patients. The study was performed during a period of 4 months and we did not observe any patient re-entering into the hospital because of the presence of a new episode of uterine activity. Whether the patients underwent another period of uterine activity and received medical care in another hospital or successfully completed the pregnancy period, cannot be clarified in our study. Also, the fetal and maternal long-term morbidity was unknown. Obstetrician service is the main request of medical care in Mexican hospitals, and births have been 31.2% of total hospital discharges, being 53.9% of total births registered in 1997 attended at the IMSS [9]. A careful selection of pregnant women in order to avoid a dangerous impact to both or either the mother and the fetus due to the production of palpitations counterbalancing the benefits between its use for managing a threatened abortion or a premature labor and costs of minor ADR's, must be mandatory. Furthermore, the small range of current options to be used as tocolytics should stimulate this area in order to identify drugs with lesser production of side effects. In fact, terbutaline could not only be undangerous for the fetus but to promote neonatal respiration and metabolic adaptation after elective cesarean section and to reduce the number of fetal heart abnormalities [33,34].

In relation to indomethacin, this drug has proved safety and efficacy to inhibit uterine contractions of premature labor [35,36]. Uterine contractility at term and preterm results from an activation of myometrium through several process varying from mechanical stimulation to a complex cascade of endocrine processes [37]. Prostaglandinds are important regulators of the labor process [38], and therefore its manipulation has resulted into a direct effect favoring or inhibiting uterine activity [39,40]. However, it is well known the adverse effects of all nonsteroidal antiinflamatory drugs administered at the third trimester of pregnancy [41–43], including constriction of the ductus arteriosus, persistent fetal circulation, impairment of renal function and bleeding. Furthermore, brain maldevelopment and neurobehaviour deviations have been experimentally demonstrated after neonatal exposure to indomethacin [44]. Therefore, despite our results seem likely to favour indomethacin administration because it was better tolerated than terbutaline for tocolysis, the serious adverse effects potentially produced in the fetus by indomethacin make this drug a greatly dangerous option for preterm labor management.

Additionally, incidence of preterm birth is greatly increased among the socially disadvantaged women, probably explained by two major factors [45]. First, the presence of chronic and acute social stressors which in turn are translated into organc responses. Second, the presence of

a gene-environment interaction based on a highly prevalence mutation in the gene for methylentetrahydrofolate reductase. Even more, maternal education level could decrease infant mortality rate by preventing preterm births [46], without affecting fetal growth [47]. In the present study, most patients have the basic education level, and therefore if any effect was present this would be protector. Finally, there is a need for a simple, efficient and low-cost of ADR's reporting system covering a wide range of the population receiving any drug. The spontaneous reports probably satisfy these conditions and participation of nurses in the design of strategies of recognizing any ADR is undoubtedly necessary [48,49].

In conclusion, terbutaline was responsible of a high rate of mild ADR's in women receiving this drug as a tocolytic agent. However, the lack of well recognized options makes terbutaline the major tocolytic drug currently available.

Competing interests

None declared

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References

1. Olsson S: **The role of the WHO program on International Drug Monitoring in coordinating wolrdwide drug safety efforts.** *Drug Saf* 1998, **19:**1-10
2. Lazarou J, Pomeranz BH, Corey PN: **Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.** *JAMA* 1998, **279:**1200-1205
3. Detournay B, Fagnani F, Ouyanne P, Haramburu F, Begaud B, Welsch M, Imbs JL: **Cost of hospitalizations related to side-effects drugs (*in French*).** *Thérapie* 2000, **55:**137-139
4. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP: **Adverse drug events in hospitalized patients. Excess lenght of stay, extra costs, aand attributable mortality.** *JAMA* 1997, **277:**301-306
5. Walson PD: **Therapeutic drug monitoring in special populations.** *Clin Chem* 1998, **44:**415-419
6. Ghandour FZ, Knauss TC, Hricik DE: **Immunosuppressive drugs in pregnancy.** *Adv Ren Replace Ther* 1998, **5:**31-37
7. Becerril-Marténez MC, Díaz-Marténez A, Bondani-Guasti A: **Introducción a la farmacovigilancia.** *México DF, Secretaría de Salud,* 1995, 13-14
8. Instituto Nacional de Estadística, Geografía e Informática: **XII Censo General de Población y Vivienda 2000: Síntesis de Resultados.** *IAEGI: Estados Unidos Mexicanos* [http://www.inegi.gob.mx]
9. Secretaría de Salud, Dirección General de Estadística e Informática del Sistema Nacional de Salud, Sistema Sectorial de Información en Salud: **Principales servicios de hospitalización por institución de salud.** *Bol Inform Estad* 1997, **1:**25-43
10. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, Newhouse JP, Weiler PC, Hiatt HH: **Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I.** *N Eng J Med* 1991, **324:**370-376
11. Caranasos GJ, Stewart RB, Cluff LE: **Drug-induced illness leading to hospitalization.** *JAMA* 1974, **228:**713-717
12. Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR: **An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use.** *JAMA* 1979, **242:**623-632
13. Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR: **An algorithm for the operational assessment of adverse drug reactions. II. Demonstration of reproducibility and validity.** *JAMA* 1979, **242:**633-638
14. Leventhal JM, Hutchinson TA, Kramer MS, Feinstein AR: **An algorithm for the operational assessment of adverse drug reactions. III. Results of tests among clinicians.** *JAMA* 1979, **242:**1991-1994
15. Vargas-Rivera J, Hernández HDM, Sumano LH, Palma AA, Bondani GA, Ponce MH: **Reacciones adversas a los medicamentos en pacientes pediátricos en dos hospitales de segundo nivel.** *Rev Med IMSS* 1996, **34:**421-427
16. Elwood MJ: **Critical appraisal od epidemiological studies and clinical trials.** *New York, Oxford University Press* 1998, 104-108
17. Landis JR, Koch GG: **The measurement of observer agreement for categorical data.** *Biometrics* 1977, **33:**159-174
18. Capellá D, Laporte JR: **Spontaneous notification of adverse drug reactions (*in Spanish*).** *In: Phncipios de epidemiología de los medicamentos* 1993, 147-170
19. Venulet J, Bankowski Z: **Harmonising adverse drug reaction terminology: the role of the Council for International Organizations of Medical Sciences.** *Drug Saf* 1998, **19:**165-172
20. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR: **Causal or casual? The role of causality assessment in pharmacovigilance.** *Drug Saf* 1997, **17:**374-389
21. Mariani L, Minora T, Ventresca GP: **Drug surveillance and adverse reactions to drugs. The literature and importance of historical data (*in Italian*).** *Clin Ter* 1996, **147:**653-672
22. Mariani L: **Pharmacovigilance: education and continuing updating. The role of university institutes (*in Italian*).** *Clin Ter* 1998, **149:**219-225
23. Thurmann PA, Schmitt K: **Detection and evaluation of adverse drug effects (*in German*).** *Med Klin* 2000, **95:**4-8
24. Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD: **Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies.** *Br J Clin Pharmacol* 1998, **46:**505-511
25. Ciorciaro C, Hartmann K, Kuhn M: **Differences in the relative incidence of adverse drug reactions in relation to age? An evaluation of the spontaneous reporting system of SANZ (Swiss Drug Monitoring Center) (*in German*).** *Schweiz Med Wochenschr* 1998, **128:**254-258
26. Muñoz MJ, Ayani I, Rodriguez-Sasiain JM, Gutiérrez G, Aguirre C: **Adverse drug reaction surveillance in pediatric and adult patients in an emergency room (*in Spanish*).** *Med Clin (Barc)* 1998, **111:**92-98
27. Tran C, Knowles SR, Liu BA, Shear NH: **Gender differences in adverse drug reactions.** *J Clin Pharmacol* 1998, **38:**1003-1009
28. Classen DC, Pestotnik SL, Evans RS, Burke JP: **Computerized surveillance of adverse drug events in hospital patients.** *JAMA* 1991, **266:**2847-2851
29. Uppal R, Jhaj R, Malhotra S: **Adverse drug reactions among inpatients in a north Indian referral hospital.** *Natl Med J India* 2000, **13:**16-18
30. Lam F, Elliott J, Jones JS, Katz M, Knuppel RA, Morrison J, Newman R, Phelan J, Willcourt R: **Clinical issues surrounding the use of terbutaline sulfate for preterm labor.** *Obstet Gynecol Surv* 1998, **53(suppl):**S85-S95
31. Perry KG Jr, Morrison JC, Rust OA, Sullivan CA, Martin RW, Naef RW 3rd: **Incidence of adverse cardiopulmonary effects with low-dose continuous terbutaline infusion.** *Am J Obstet Gynecol* 1995, **173:**1273-1277
32. Gyetvai K, Hannah ME, Hodnett ED, Ohisson A: **Tocolytics for preterm labor: a systematic review.** *Obstet Gynecol* 1999, **94:**869-877
33. Kulier R, Hofmeyr GJ: **Tocolytics for suspected intrapartum fetal distress.** *Cochrane Database Syst Rev* 2000, **2:**CD000035
34. Eisler G, Hjertberg R, Lagercrantz H: **Randomised controlled trial of effect of terbutaline before elective caesarean section on**

postnatal respiration and glucose homeostasis. *Arch Dis Child Fetal Neonatal Ed* 1999, **80:**F88-F92
35. Katz Z, Lancet M, Yemini M, Mogilner BM, Feigl A, Ben-Hur H: **Treatment of premature labor contractions with combined ritodrine and indomethacine.** *Int J Gynaecol Obstet* 1983, **21:**337-342
36. Morales WJ, Smith SG, Angel JL, O'Brien WF, Knuppel RA: **Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor: a randomized study.** *Obstet Gynecol* 1989, **74:**567-572
37. Challis JR, Lye SJ, Gibb W, Whittle W, Patel F, Alfaidy N: **Understanding preterm labor.** *Ann N Y Acad Sci* 2001, **943:**225-234
38. Zakar T, Hertelendy F: **Regulation of prostaglandins synthesis in the human uterus.** *J Matern Fetal Med* 2001, **10:**223-235
39. Frohn WE, Simmons S, Carlan SJ: **Prostaglandin E2 gel versus misoprostol for cervical ripening in patients with premature rupture of membranes after 34 weeks.** *Obstet Gynecol* 2002, **99:**206-210
40. Scott JE, Grigsby PL, Hirst JJ, Jenkin G: **Inhibition of prostaglandin synthesis and its effect on uterine activity during established premature labor in sheep.** *J Soc Gynecol Investig* 2001, **8:**266-276
41. Ostensen M, Ramsey-Goldman R: **Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options?** *Drug Saf* 1998, **19:**389-410
42. Weintraub Z, Solovechick M, Reichman B, Rotschild A, Waisman D, Davkin O, Lusky A, Bental Y: **Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight infants.** *Arch Dis Child Fetal Neonatal Ed* 2001, **85:**F13-F17
43. Cuzzolin L, Dal-Cere M, Fanos V: **NSAID-induced nephrotoxicity from the fetus to the child.** *Drug* 2001, **24:**9-18
44. Benesova O, Tejkalova H, Kristofikova Z, Husek P, Nedvidkova J, Yamamotova A: **Brain maldevelopment and neurobehavioural deviations in adult rats treated neonatally with indomethacin.** *Eur Neuropsychopharmacol* 2001, **11:**367-373
45. Kramer MS, Goulet L, Lydon J, Seguin L, McNamara H, Dassa C, Platt RW, Chen MF, Gauthier H, Genest J, Kahn S, Libman M, Rozen R, Masse A, Miner L, Asselin G, Benjamin A, Klein J, Koren G: **Socioeconomic disparities in preterm birth: causal pathaways and mechanisms.** *Pediatr Perinatal Epidemiol* 2001, **15(suppl 2):**104-123
46. Scott-Wright AO, Wrona RM, Flanagan TM: **Predictors of infant mortality among college-educated black and white women, Davidson County, Tennessee, 1990–1994.** *J Natl Med Assoc* 1998, **90:**477-483
47. Zeitlin JA, Ancel PY, Saurel-Cubizolles MJ, Papiernik E: **Are risk factors the same for small for gestational age versus other preterm births?** *Am J Obstet Gynecol* 2001, **185:**208-215
48. Arnold GJ: **Clinical recognition of adverse drug reactions: obstacles and opportunities for the nursing profession.** *J Nurs Care Qual* 1998, **13:**45-55
49. Morrison-Griffiths S, Pirmohamed M, Walley T: **Reporting of adverse drug reactions: practice in the UK.** *Nurs Times* 1998, **94:**52-54

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