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ORIGINAL ARTICLE

Utility of Free Web-Based Software for Identifying Potentially Teratogenic Medicines in Pregnancy

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Abstract

Aim & Objective: To study and validate the clinical utility of free web-based software in picking up potentially and clearly harmful prescribed medicines with reference to FDA category.**Materials and Methods:** The present observational, cross-sectional, prospective, web-based prescription audit study was carried over a period of one year in a tertiary care teaching hospital. A total of 500 such prescriptions prescribed to pregnant women coming for routine antenatal checkup, irrespective of month of gestation, from any socioeconomic/ socio-demographic background were collected for one-point analysis. The analysis was carried out to evaluate specificity, sensitivity, positive predictive value and negative predictive value. **Results:** A total number of 1588 drugs were prescribed for 500 prescriptions studied with a mean of 3.17. Web-based free software picked up 1383 (87.09%) drugs, while rest 205 (12.91%) drugs were not picked up by the software. Potential teratogenic effect picked up by the software included 468 (29.48%) drugs. The sensitivity of software with reference to four textbooks varied from 70.76% to 60.32%, specificity 99.04% to 97.18%, positive predictive 98.29 to 94.87% and negative predictive value from 74.10% to 73.92%.**Conclusion:** Validation of drugs picked-up by the software as potential teratogenic was suboptimal as per sensitivity, specificity and accuracy were concerned.

Key Words

Community-acquired pneumonia, Hyponatremia, CURB 65 score

Introduction

Medication use is very common during pregnancy due to various medical ailments.[1] The safety of use of medicines during pregnancy is, however, not always clear because majority of medicines lack sufficient data for teratogenicity and impact on maternal health.[2] The drugs that are safe for adult may prove tetratogenic for in-womb foetus. Majority of medicines or their metabolites have potential to cross placental barrier because placenta is an incomplete barrier & the drugs have effect on DNA, RNA, protein, chromosomes and enzymes as well as direct cytotoxic effect known to induce fetotoxic effect .[3] The drug factors like the dose, duration, route, frequency of drug use, and maternal factors like medical condition, nutritional status of mother and gestational age also determines the foetotoxicity.[4]

On review of literature, there is paucity of research in

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this particular field which deals with the safe drug use during pregnancy and medical information used by the patient and doctors to enhance the drug safety in pregnancy.[5]

The safefetus.com is a web-based free software which is complete data based (generic and trade name) providing information on drugs in respect to indication, foetus risk, risk during pregnancy according to FDA. It also depicts the possible mechanism and level of risk a drug is likely to cause in a foetus during pregnancy.[6]

The present research was conceived to find out utility of this medical software in clinical practice. The result of this research is going to be of eminent clinical importance. The software is a free and compatible in smart phones which clinicians can use very often whenever they are in dilemma while prescribing drugs in pregnant females.

Materials and Methods

The present observational, cross-sectional, prospective, web-based prescription audit study was carried over a period of one year in a tertiary care teaching hospital. The prescriptions were collected by an independent person by clicking the picture by mobile phone outside Obstetrics OPD without the knowledge of prescriber to avoid any bias after due administrative and Institutional Ethical Committee's permission.

A total of 500 such prescriptions prescribed to pregnant women coming for routine antenatal checkup, irrespective of month of gestation, from any socioeconomic/ sociodemographic background, all medical conditions for which medicines were prescribed, including all acute or chronic medical illness, all fixed dose combination medication personally were identified and collected for one-point analysis.

Patients were excluded if they were indulging in self medication, using herbal medicine, over the counter used medicine, nutraceutical medicine or were prescribed vaccination.

A sociodemographic profile of the pregnant women, background information, health disorders and use of medicine during pregnancy, average number of medicines per prescription, prescription with correct dose strength and dose schedule, number of prescription mentioning duration of therapy, over prescribing, banned medicine formulation, medicines with combination, disputed pharmacological rationale, generic and fixed medicine combination prescription rate were evaluated.

Every medicine prescribed was noted in generic names and then every prescription individually was evaluated with the help of web-based safefetus.com software. The selection of free software was based on preliminary survey carried out by giving questionnaire asking most commonly used software for assessing foetal risk (as per FDA guideline). The information provided by this software on foetus risk according to FDA categorization along with potential mechanism to cause foetus risk was noted. To validate the utility of information retrieved for every respective medicine, the information was compared with standard references (Goodman and Gillman's Pharmacological Basis of Therapeutics, Williams Obstetrics, Nelson Textbook of Pediatrics, Applied Therapeutics - The Clinical Use of Drugs) to work out the specificity, sensitivity and positive and negative predictive value of this software.

The FDA assigned pregnancy categories as used in the Drug Formulary are as follows: Category A (controlled studies show no risk); Category B (no evidence of risk in humans); Category C (risk cannot be ruled out); Category D (positive evidence of risk); and Category X (contraindicated in pregnancy). [7]

All the principles of bioethics were adopted. Verbal informed consent was taken as present study falls in least risk category and is an observational study (as per the ICMR Research Code).The name of the drugs was used by generic name. Name of the prescriber and of patient was not enrolled for all practical purposes to avoid any conflict of interest.

Statistical analysis

All data were reported as frequency/percentage. The analysis was carried out with the help of computer softwares MS Excel and IBM SPSS version 23 for Windows to evaluate specificity, sensitivity, positive predictive value and negative predictive value.

Results

A total number of 1588 drugs with a range of 1 to 7 were prescribed for 500 prescriptions studied. Average number of drugs prescribed was calculated to be 3.17. The mean age of the subjects was 25.58 years with a range of 19 to 38 years. A total of 511 medical disorders were observed in 500 prescriptions in the study. The major medical disorders were pain abdomen (17.41%), antenatal cases (17.22%), nausea (12.13%), fever (4.89%), discharge P/V and hypothyroidism (4.50% each) and vomiting (3.91%). There were 48 other medical disorders with frequency varying from 1 to 18.

Most of the drugs prescribed were calcium salts (256; 16.12%), iron salts (239; 15.05%) and folic acid (116; 7.30%). Other than these, a total of 100 different drugs were prescribed with different frequencies (*Table 1*).

Table 1. Study Profile

Total prescriptions studied, no.		500
Total drugs prescribed (Range), no.		1588 (1 – 7)
Average drugs prescribed, %		3.17
Mean age of subjects (Range), years		25.58 ± 3.30 (19 – 38)
Urban-Rural ratio		13.71:1
Primi/Multigravida, %		61/39
Nulli/Multiparous, %		72.80/27.20
Medical disorders, %	**Pain abdomen**	17.41
	Nausea	12.13
	Fever	4.89
	Discharge P/V	4.50
	Hypothyroidism	4.50
	Vomiting	4.50
	Others	52.64
Drugs prescribed, %	**Calcium containing salts**	16.12
	Iron containing salts	15.05
	Folic acid	7.30
	Isoxspuine	4.65
	Doxylamine	4.34
	Progesterone	4.21
	Pyridoxine	3.21
	Pantaperazole	2.58
	Others	42.51

Table 2. Potential Teratogenic Effect Picked up by the Software (n=1588)

Potential teratogenic effect	No. (%)
Present	468 (29.48)
Absent	319 (20.08)
Data not available	596 (37.53)
Not picked up by software	205 (12.91)
Total	**1588 (100.00)**

Table 3. Distribution of FDA Risk Category in Pregnancy as Picked up by the Software (n=1588)

FDA risk category in pregnancy as picked up by the software	No. (%)
A	271 (17.06)
B	218 (13.72)
C	174 (10.95)
D	111 (6.98)
X	4 (0.25)
FDA risk category in pregnancy as picked up by the software	778 (48.99)
Not classified	605 (38.10)
Not picked up by software	205 (12.91)

Dose was mentioned for 1542 (97.10%) drugs, route of administration was mentioned for 1582 (99.62%) drugs and dosage form was available for all drugs. Duration of treatment was mentioned for 1547 (97.42%) drugs, while dosage schedule was mentioned for 1584 (99.75%) drugs.

Potential teratogenic effect picked up by the software

included 468 (29.48%) drugs. Potential teratogenic effect reported absent by the software included 319 (20.08%) drugs. Data for potential teratogenic effect was not available for 596 (37.53%) drugs (*Table 2*).

Web-based free software, safefetus.com, picked up 1383 (87.09%) drugs, while rest 205 (12.91%) drugs were not picked up by the software. FDA risk categories A, B, C, D, X were identified in 271 (17.06%), 218 (13.72%),

Table 4. Potential Teratogenic Effect Picked up by the Software, Confirmed and Validated by Standard Reference Textbooks (n=1383)

Standard reference textbooks	Validated No. (%)	Not validated No. (%)
Goodman and Gillman's	750 (54.23)	633 (45.77)
Williams Obstetrics	740 (53.51)	643 (46.49)
Nelson's Textbook of Paediatrics	707 (51.12)	676 (48.88)
Applied Therapeutics	736 (53.22)	647 (46.78)

Table 5. Relation of Teratogenic Effect Picked Up by the Software & Validated by Four Standard Books

Variables	Goodman and Gillman's	Williams Textbook	Nelson Textbook	Applied Therapeutics Textbook
True positive	460	461	430	444
True negative	830	841	843	824
False positive	8	7	38	24
False negative	290	279	277	292
Sensitivity	70.76%	62.16%	60.82%	60.32%
Specificity	99.04%	99.17%	95.68%	97.18%
Positive predictive value	98.29%	98.71%	91.88%	94.87%
Negative predictive value	74.10%	75.05%	75.26%	73.92%
False positive rate (FPR)	0.95	0.83	4.31	2.82
False negative rate (FNR)	38.67	37.71	39.18	39.68
False discovery rate (FDR)	1.71	1.50	8.12	5.13
Accuracy	81.23	81.99	80.16	80.10
F1 Score	75.53	76.32	73.20	73.75
Matthew Corr Coeff	0.00	0.00	0.00	0.00
Informedness	60.38	61.48	56.51	57.51
Markedness	-75.82	-76.59	-83.39	-79.06
Power	61.33	62.30	60.82	60.33
Likelihood Ratio Positive	64.25	75.47	14.10	21.42
Likelihood Ratio Negative	0.40	0.39	0.41	0.41

174 (10.95%), 111 (6.98%) and 4 (0.25%) respectively, a total of 778 (48.99%) out of 1588 drugs. However, there were 605 (38.10%) drugs which were not classified by the software (*Table 3*).

When potential teratogenic effect picked up by the software (n=778) plus those not classified (n=605; total=1383) were compared with those reported by standard reference textbooks, Goodman Gillman's validated 750 (54.23%), Williams Obstetrics validated 740 (53.51%), Nelson's Textbook of Paediatrics validated 707 (51.12%) and Applied Therapeutics validated 736 (53.22%) drugs (*Table 4*).

Correlation of potential teratogenic effect picked up by the software and validated by the Goodman Gillman's standard reference textbook was better when compared with those of Williams, Nelson's and Applied Therapeutic standard textbooks. The sensitivity of software with reference to four textbooks varied from 70.76% to 60.32%, specificity 99.04% to 97.18%, positive predictive 98.29 to 94.87% and negative predictive value from 74.10% to 73.92% (*Table 5*).

Discussion

Average number of drugs prescribed in the present study was 3.17, which is in agreement with Joshi *et al*. who reported average number of drugs prescribed to be 3.01 [8], while Puranik et al. reported that women used an average of 4.7 drugs during pregnancy [9] , which is higher as compared to present study.

The mean age of the subjects in the present study was 25.58 years with a range of 19 to 38 years, which is comparable to that of Joshi *et al*. [8] and Al-Riyami *et al*. [10]

The major medical disorders in the present study for which medicines were prescribed were pain abdomen (17.38%), antenatal cases (17.91%), nausea (12.11%), fever (4.88%), discharge P/V (4.49%),while Joshi *et al*. found most common complaints to be abdominal pain (13.8%) and vomiting (12.4%) followed by fever (7.5%), cough (3.4%), urinary tract infection (2.7%) and discharge per vagina (2.6%). [8]

In the present study, most prescribed drugs were calcium salts (16.12%), iron salts (15.05%), folic acid (7.30%). A total of 100 (6.29%) different drugs were prescribed with different frequencies. Dose was mentioned for 1542 (97.10%) drugs. Route of administration was mentioned for 1582 (99.62%) drugs. Dosage form was mentioned for all 1588 (100%) drugs prescribed. Duration of treatment was mentioned for 1547 (97.42%) drugs. Dosage schedule was mentioned for 1584 (99.75%) drugs.

Puranik SB *et al*. [9] while reviewing 13 studies to gather information on drug utilization patterns during pregnancy found most commonly ingested medicines were vitamins and iron preparations, analgesics, antiemetics and antacids. They added that drugs were prescribed to most women, even when vitamins, minerals, iodide and iron were omitted. Magnesium and iron seemed to have been over-prescribed, while on the other hand, the official recommendation for iodide substitution, to prevent thyroid diseases in mother and child, was insufficiently implemented, which is similar to the present study.

Out of 1588 drugs, software picked up 1383 (87.09%) drugs. Rest 205 (12.91%) drugs were not picked up by software. Software picked up 778 (48.99%) FDA risk categories drug (A, B, C, D, X) in pregnancy out of a total of 1588 drugs. There were 605 (38.10%) drugs which were not classified by software and others 205 (12.91%) were not picked up by software. Teratogenic effect picked up by software included 468 (29.48%) drugs. Software picked up 271 (17.06%) category A drugs, 218 (13.2%) category B drugs, 174 (10.95%) category C drugs, 111 (6.98%) category D drugs and 4 (0.25%) category X drugs.

Cleary BJ *et al*. [11] reported FDA category D and X medications by 1532 (2.5%) and 1987 (3.2%) women in their study of 61252 cohort, wherein extent, nature and determinants of medication use in early pregnancy was reviewed. Compared to the present study, this study reported less number of category D drugs, while category X drugs were significantly more. Difference could be because this study was done in a large group of population as compared to the present study.

The results of the current study are almost similar to the findings of the study of Robert D. Beckett RD *et al*. [12] , where in the utility of various Drug Information software were studied in a cross-sectional evaluation like Facts & Comparisons eAnswers, Lexicomp Online, Micromedex, Drug Interactions Analysis and Management, Drug Interaction Facts, and Stockley's Drug Interactions and results suggested that Scope scores ranged from 0.6% (Drug Interactions Analysis and Management) to 43.4% (Lexicomp Online). Completeness scores ranged from 2 (interquartile range [IQR] 0 to 3, Stockley's Drug Interactions) to 5 (IQR 5 to 5, Drug Interaction Facts, Micromedex, Facts & Comparisons eAnswers). Consistency scores ranged from 30.8% (Stockley's Drug Interactions) to 87.1% (Clinical Pharmacology) for severity and from 15.4%

(Facts & Comparisons eAnswers) to 71.4% (Drug Interaction Facts) for course of action. Thereby, suggesting drug-DoA interactions was low and content was often inconsistent among resources, the provided information was generally complete like our study.

However, the results of the current study were in contradiction with the study of Shariff A *et al* [13] , studied the utility of providing complete drug information by total of eight DI resources, namely, Micromedex®, Portable Electronic Physician Information Database©, UpToDate®, Medscape.com drug interaction checker, Drugs.com drug interaction checker, Stockley's Drug Interactions , Drug Interactions Analysis & Management. Their study suggested that the inter-source reliability scores among the eight different DI sources were poor ($k < 0.20$, $p < 0.05$) for documentation of information related to severity, clinical effects, mechanism, and management of DDIs. Variations in the information cause uncertainty among healthcare professionals concerning interacting drug pairs in clinical practice. This may also increase the possibility of adverse drug outcomes when interacting drug pairs are used in at-risk patients.

In a systematic review, utility of various software was studied and unlike the results of our study deficiency of clinical relevance was suggested to be major draw back of these software in providing drug Information. [14]

In purview of the results of safefetus.com software used in the current study which showed relatively low sensitivity in reference to various standard sources of drug information, the same software at present cannot be advocated to healthcare providers for providing complete scientific, evidence-based and valid information.

Conclusion

The free web-based software could pick up substantial number of drugs with potential teratogenicity among different drugs prescribed during antenatal period. However, the study observed that validation of drugs picked-up by the software as potential teratogenic was suboptimal as per sensitivity, specificity and accuracy were concerned. Hence, at present the said software may not be advocated to healthcare providers for complete evidence-based scientific information for potential teratogenic drugs and thus needs up-gradation.

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Conflicts of Interest
There are no conflicts of interest.

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