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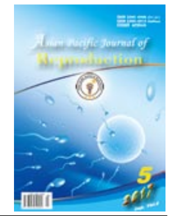

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An online infertility clinical decision support system

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ABSTRACT

Objective: To explore some possibilities of computer applications in medicine, and to discuss an online infertility clinical decision support system. **Methods:** Retrospective data were obtained from 52 couples, and then entered into the online tool. Both its results and the initial diagnoses obtained by the treating physicians were compared with the final diagnoses established by laparoscopy and other diagnostic tests (semen analysis, hormone analysis, endometrial biopsy, ultrasound and hysteroscopy). The initial hypothesis of the research was that the online tool's output was statistically associated with the final diagnoses. In order to verify that hypothesis, a *chi*-square (χ^2) test with Yates' correction for continuity ($P<0.05$) was performed to verify if the online tool's and the doctor's diagnoses were statistically associated with the final diagnoses. **Results:** Four etiological factors were present in more than 50% of the couples (ovarian, tubal-peritoneal, uterine, and endometriosis). The statistical results confirmed the research hypothesis for eight out of the nine etiological factors (ovarian, tubal-peritoneal, uterine, cervical, male, vaginal, psychosomatic, and endometriosis; $P<0.05$). Since there were no cases related to the immune factor in the sample, further clinical data are necessary in order to assess the online tool's performance for that factor. **Conclusions:** The online tool tends to present more false-positives than false-negatives, whereas the expert physician tends to present more false-negatives than false-positives. Therefore, the online tool and the doctor seem to complement each other. Finally, the obtained results suggest that the infertility online tool discussed herein might be a useful research and instructional tool.

1. Introduction

The future of medicine and healthcare cannot be imagined without considering an extensive use of computer applications. As a matter of fact, computers are already present in the daily lives of physicians, as well as in the routines of other healthcare professionals[1-5].

Computer applications can be used as tools to assist healthcare professionals in delivering better and safer healthcare services to patients, and also as an aide for their professional development and training. In fact, recent publications have discussed some types of computer applications in medicine that have showed potential to improve the quality of healthcare delivered to patients and reduce the occurrence of medical errors and adverse drug events[1-5].

Some examples of computer applications in medicine and healthcare are: electronic medical records, bar-code-enabled & point-of-care systems, computerized physician order entry (CPOE) systems, automated medication administration records, and clinical decision support systems (CDSS)[1-5].

Electronic medical records are computerized medical information systems that collect, store and display patient information, and

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they are also a means to create legible and organized recordings and to access clinical information about individual patients[1]. Moreover, electronic medical records are intended to replace existing (often paper based) medical records which are already familiar to practitioners[1].

The bar-code-enabled & point-of-care systems are advanced systems using touch screen and barcode scanning technology to provide full information on medication orders, patient problems, treatment history, clinical observations, blood or tissue samples withdrawal, transfusion orders, and so on[2].

The CPOE systems are basically computer systems that deal with electronic entry of physician's instructions and orders for treating hospitalised patients[2,3]. Moreover, some hospitals have implemented CPOE systems to reduce the medical error rates[4].

The ease of use of a CPOE system and the quality of information can significantly reduce prescribing errors. CPOE systems can also reduce the likelihood of drug allergy, drug interaction, and drug dosing errors thus improving patient safety[4]. Furthermore, prescribing errors in terms of drug allergy, drug interaction, and drug dosing errors are reduced if the CPOE is not error-prone and easy to use, if the user interface is consistent, and if it provides quality information to doctors[4].

CDSS can be any kind of computerized tool designed to impact clinician decision making about individual patients at the point in time that these decisions are made[5]. CDSS have also been a key element of systems' approaches to improve patients' safety and the quality of care[5].

On the one hand, one particular kind of CDSS is called expert system, which can be defined as an intelligent computer program that uses knowledge and inference procedures to solve problems that are difficult enough to require significant human expertise for their solutions[6].

On the other hand, the desire to have children is a very important issue for most couples, and childlessness can have a profound impact on their lives. One of the major factors of childlessness is infertility, that is, the inability to conceive after a year or more of trying and resulting in involuntary childlessness[7].

Regarding the study of computer applications in reproductive medicine, some researchers have recently designed and/or developed expert systems with the objective of diagnosing the causes of infertility[8–11]. Following that scientific trend, InfertQuiz (http://infertquiz.awardspace.com/) is an online expert system that is designed and implemented to identify the etiological factors of infertility.

Thus, the objective of this study was to overview some of the possibilities of computer applications in medicine, and to discuss the InfertQuiz infertility online tool. The tool is an example computer application in reproductive medicine, which will be introduced in detail in the following sections of this article.

2. Materials and methods

This section described the architecture of the online tool, which was composed of the inference engine, the knowledge base, the knowledge representation, the output presented by the online tool, the database, and the user interface. Afterwards, the clinical test conducted in order to validate the online tool was also described.

2.1. Online tool architecture

The software used to develop the online tool was PHP[12]. Its architecture is composed by the following elements: inference engine, knowledge base, database, and user interface. Each of these elements is described below, as well as the knowledge representation technique that was used, the output presented by the system, and the summary of the clinical test that was performed.

2.2. Inference engine

This part of the online tool controlled the user interface, the knowledge base and the database. It used the forward-chaining technique in order to come to the output, *i.e.* it started with some facts (symptoms or inputs) and applied rules to find all possible conclusions (diagnoses or outputs)[13].

2.3. Knowledge base

The author adapted and updated the knowledge base from an expert system originally developed by Dr. Álvaro Petracco (expert system in couple sterility, presented in the 18th Brazilian Congress of Human Reproduction, Porto Alegre, Brazil, 1988). This adaptation was performed with the assistance of Dr. Marco Cavalcanti (Clínica Reprodução, Aracaju, Brazil). The author conducted 10 interviews with Dr. Marco Cavalcanti in order to acquire the knowledge that was used to adapt and update the knowledge base[14]. The knowledge base contained 115 rules[14].

2.4. Knowledge representation

The knowledge was represented using if-then rules, also called production rules. This methodology was chosen because amongst the different methods for representing the knowledge, production rules were the most frequently used for diagnostic expert systems[15], and also because it was easy to represent the accumulated experience of an expert in a certain field of knowledge using if-then rules, which would be used afterwards for applying the knowledge base to a particular situation[16].

In fact, rule-based expert systems were one of the most common applications of Artificial Intelligence[8]. Moreover, it was also easy to change, to adapt or to eliminate existing rules, as well as to add new ones. The following rules were two examples of the actual online tool's rules (the reader should note this is not actual PHP code):

IF symptom = woman's age > 45
THEN conclusion = ovarian factor (score = 4)
IF symptom = man uses drugs
THEN conclusion = male factor (score = 4)

First, the user introduced the symptoms in the database using the user interface. After that, the online tool used those symptoms to evaluate all the if-then rules. If the condition in the first part of each rule was found true, the associated conclusion was then stored in the database together with an associated score. The conclusions can be related to any combination of nine possible etiological factors: ovarian, tubal-peritoneal, uterine, cervical, immune, male, vaginal, psychosomatic and endometriosis.

The score based on information extracted from the knowledge that came from the human experts' experience, represented a measure of the uncertainty of that diagnostic conclusion. For all the rules, each conclusion had an associated score, which ranged from 1 to 5. The respective qualitative meanings of each score are:

a) Almost improbable (score = 1);

b) Not so probable (score = 2);

c) Probable (score = 3);

d) Highly probable (score = 4);

e) Almost sure (score = 5).

These standard scores and qualitative meanings were established according to the combined experience and knowledge of the above-mentioned expert physicians for each of the online tool's production rules.

2.5. Output presented by system

Depending on the specific clinical data, the system can find more than one conclusion containing the same etiological factor. In that case, the online tool will combine all the conclusions containing the same etiological factor in order to generate a single conclusion using the technique of uncertainty reduction[17]. This technique was used in the expert systems MYCIN and EMYCIN, and is considered as one of the most acceptable ways of combining scores in rule-based expert systems[17].

Using the abovementioned technique, the online tool combined all the conclusions that contained the same etiological factor and presented the final conclusions using the qualitative meanings, according to their final scores, as follows:

a) Almost improbable: final score $<$ 1.5;

b) Not so probable: 1.5 $\leqslant$ final score $<$ 2.5;

c) Probable: 2.5 $\leqslant$ final score $<$ 3.5;

d) Highly probable: 3.5 $\leqslant$ final score $<$ 4.5;

e) Almost sure: final score $\geqslant$ 4.5.

It's worth mentioning that this rounding technique was totally consistent with the definitions of the qualitative meanings and the corresponding scores mentioned before when the knowledge representation was discussed.

2.6. Database and user interface

The database was constructed when the user interacted with the system and answered the 119 questions about the infertile couple. The data obtained from a questionnaire (user interface) was then used to build the database.

2.7. Clinical test

First of all, it was worth remarking that even though the total worldwide population of infertile people was very difficult to estimate, infertility remained a problem of global proportions[18]. Secondly, some researchers have tried to estimate different percentages of infertile couples. For example, there was an estimate that about 15% of all couples were infertile[19], but other researchers affirmed that approximately 10%-15% of couples in their reproductive age involuntarily suffer childlessness[20].

Moreover, some other researchers considered that infertility was still a highly prevalent global condition, which was estimated to affect between 8%-12% of reproductive-aged couples worldwide[21,22].

On the other hand, some studies stated that infertility equally affected men and women[23]. Therefore, infertility can be regarded as a health problem which was widespread all over the world, and a complete investigation of the infertile couples was needed in order to identify all the possible etiological factors.

The clinical cases used in this study came from a sample of 52 infertile couples randomly selected among patients treated by Dr. Marco Cavalcanti (Clínica Reprodução, Aracaju, Brazil; 26 couples), Dr. Juergen Eisermann (South Florida Institute Reproductive Medicine, Miami, USA; 13 couples) and Dr. Alberto Costoya (Universidad de Santiago de Chile, Santiago, Chile; 13 couples)[14]. Their clinical data were collected between January and July, 1997. In addition, the research protocol was approved by the institutional review board of Universidade Federal da Paraíba (João Pessoa, PB, Brazil)[14].

The women's ages ranged from 23 to 47 years old, with an average of 35 years old. The men's ages ranged from 25 to 48 years old, with an average of 38 years old. The length of infertility ranged from 1 to 20 years, with an average of 6 years.

It was important to mention that a retrospective analysis of the results obtained by the online tool was conducted in 2017 using the patient data which were collected in 1997. Afterwards, the results obtained with the use of the online tool in 2017 were compared with the doctors' diagnoses which were obtained in 1997.

For all the couples, the initial diagnoses provided by the physicians were registered, and the final diagnoses, regarding the female factors, were eventually established by laparoscopy. Additionally, some other diagnostic tests, such as semen analysis, hormone analysis, endometrial biopsy, ultrasound and hysteroscopy were conducted to evaluate both male and female factors.

For the clinical test, all clinical data were inserted into the online tool, and the results for each factor were registered. After that, a *chi*-square (χ^2) test with Yates' correction for continuity (P<0.05) was performed in order to verify whether or not the online tool's diagnoses and the doctor's diagnoses were statistically associated with the final diagnoses[24]. In order to check if the research hypothesis was verified, the *chi*-square (χ^2) parameter had to be greater than the critical value χ_c^2=3.84 (P<0.05).

3. Results

The proportion of occurrence of each factor in the set of 52 clinical cases was shown in Table 1, according to the final diagnoses established for each case. The etiological factors that were present in more than 50% of the couples were ovarian, tubal-peritoneal, uterine, and endometriosis.

Table 1
Proportion of occurrence of each etiological factor in 52-couple sample.

Etiological factor	Number of occurrences (n)	Proportion of occurrence (%)
Ovarian	27	51.92
Tubal-peritoneal	32	61.54
Uterine	29	55.77
Cervical	25	48.08
Immune	0	0.00
Male	19	36.54
Vaginal	1	1.92
Psychosomatic	3	5.77
Endometriosis	28	53.85

The analysis of the 52 clinical cases showed that for each etiological factor, there was a certain number of true-positives (TP), true-negatives (TN), false-positives (FP) and false-negatives (FN)[25]. Table 2 showed the results for the physician and the online tool that the online tool presented more FP than FN (54 cases *vs.* 21 cases), whereas the expert physician presented more FN than FP (34 cases *vs.* 20 cases). This can lead to the conclusion that the online tool and the expert doctor seem to complement each other.

Table 2
Number of TP, TN, FP, and FN in sample for each infertility etiological factor.

Etiological factor	Doctor				Online Tool			
	TP	FN	FP	TN	TP	FN	FP	TN
Ovarian	22	5	3	22	27	0	15	10
Tubal-peritoneal	23	9	3	17	28	4	6	14
Uterine	20	9	1	22	24	5	4	19
Cervical	23	2	3	24	23	2	9	18
Immune	0	0	0	52	0	0	0	52
Male	14	5	3	30	14	5	6	27
Vaginal	1	0	1	50	1	0	1	50
Psychosomatic	2	1	0	49	2	1	0	49
Endometriosis	25	3	6	18	24	4	13	11
Total	130	34	20	284	143	21	54	250

A possible explanation for this can be drawn from some of the advantages and disadvantages of expert systems, because they have a fast response and analyze all the information used as input, which could sometimes lead to overestimating the importance of some symptoms that were not so relevant and might generate FP. Furthermore, expert systems did not have the common sense that doctors possess and did not always respond appropriately to exceptional cases[16]. Conversely, doctors can possibly underestimate some symptoms they considered irrelevant at first sight, which might sometimes generate FN.

For each couple, the online tool had generally presented more than one etiological factor in the final conclusion. In order to analyze the results, the author had to perform a significance test for each etiological factor separately. The results of the statistical tests for the doctor and the online tool were shown in Table 3 (*chi*-square test with Yates' correction for continuity, χ_c^2=3.84) (P<0.05).

Table 3
Yates-corrected *chi*-square (χ^2) test results.

Etiological factor	Yates-corrected *chi*-square (χ^2) – Online tool	Yates-corrected *chi*-square (χ^2) – Doctor	χ_c^2 (critical value)
Ovarian	10.920	22.398#	
Tubal-peritoneal	15.528	13.731#	
Uterine	19.502	19.643#	
Cervical	16.479	30.815#	
Immune	-	-	3.84
Male	13.436	20.022#	
Vaginal	5.873	5.873#	
Psychosomatic	18.338	18.338#	
Endometriosis	4.824	19.593#	

#indicates that the online tool and the doctor were statistically associated considering the final diagnoses (P<0.05).

4. Discussion

The research results confirmed the initial hypothesis of statistical association between the online tool's output and the final diagnoses, since the calculated *chi*-square (χ^2) parameter with Yates' correction for continuity was greater than the critical value χ_c^2=3.84 (P<0.05) for eight out of the nine etiological factors (ovarian, tubal-peritoneal, uterine, cervical, male, vaginal, psychosomatic, and endometriosis). Regarding the immune factor, since there were no cases related to it in the 52-couple sample, further clinical data are needed in order to assess the online tool's performance related to that particular etiological factor.

Due to the fact that the online tool and the doctor were found to be statistically associated with the final diagnoses (P<0.05), the results suggest that the online tool was statistically equivalent to the expert physician. As a matter of fact, as mentioned before, the online tool and the doctor seem to complement each other. Therefore, this online tool might effectively contribute to faster and more precise diagnoses. However, further clinical data are needed in order to reinforce these results.

Regarding the similar infertility diagnosis expert systems which were mentioned previously[8–11], three of the studies did not report any kind of clinical trial[8,10,11], and one study registered that a number of doctors and patients who suffered from infertility tested the expert system and were satisfied with its efficiency[9]. However, no detail related to those tests was informed in the article[9]. Thus, the present research can be considered innovative because it documented the online expert system's design, implementation, and clinical test.

Nevertheless, it should be stressed that the online tool's objective is only to assist physicians in the process of infertility diagnosis, and its conclusions are not definite and have to be understood only as diagnostic suggestions. As a matter of fact, they may be either confirmed or rejected by the expert physicians, based on their own expertise and also on the results of the diagnostic tests.

It can be said that computer applications may become useful tools and open up a wide range of new possibilities for physicians and other healthcare professionals to improve the quality of their work. In fact, the implementation of information technologies in healthcare settings can improve the quality of care and reduce the incidence of medical errors[1–5].

Moreover, while computer applications are actually able of identifying problems and establishing links between various information sources, they are not always able of doing things that humans are better capable of doing, such as making complex decisions based on little information and communicating with each other.

Last, but not least, the potential users of this online tool can be divided into two main groups: reproductive medicine physicians, who can use it as a CDSS to help in the process of diagnosis, and medical school students, healthcare professionals, and physicians from other areas of medical expertise, who can use it as a practical tool for acquiring knowledge about infertility.

Conflict of interest statement

The author declares that he has no conflict of interest.

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References

[1] Boonstra A, Broekhuis M. Barriers to the acceptance of electronic medical records by physicians from systematic review to taxonomy and interventions. *BMC Health Serv Res* 2010; **10**: 231.

[2] Goel SD. *Textbook of hospital administration*. USA: Elsevier Health Sciences; 2014, p. 174-175.

[3] Almutairi MS, Alseghayyir RM, Al-Alshikh AA, Arafah HM, Househ MS. Implementation of computerized physician order entry (cpoe) with clinical decision support (cds) features in riyadh hospitals to improve quality of information. *Stud Health Technol Inform* 2012; **180**: 776-780.

[4] Peikari HR, Zakaria MS, Yasin NM, Shah MH, Elhissi A. Role of computerized physician order entry usability in the reduction of prescribing errors. *Healthc Inform Res* 2013; **19**(2): 93-101.

[5] Berner ES, La Lande TJ. Overview of clinical decision support systems. In: Berner E, editor. *Clinical decision support systems*. Springer, Cham: Health Informatics; 2016, p. 1-17.

[6] Sharma T, Tiwari N, Shah K. Student counseling system: A rule-based expert system based on certainty factor and backward chaining approach. *Int J Appl Innov Eng Manag* 2013; **2**(1): 371-375.

[7] Cocuzza M, Cocuzza MA, Bragais FM, Agarwal A. The role of varicocele repair in the new era of assisted reproductive technology. *Clinics (São Paulo)* 2008; **63**(3): 395-404.

[8] Robindro K, Nilakanta K. Rule-based inferencing system for infertility diagnosis in women. *Int J Artif Intell Appl* 2017; **8**(1): 1-13.

[9] Abu Naser SS, Alhabbash MI. Male infertility expert system diagnoses and treatment. *Am J Innov Res Appl Sci* 2016; **2**(4): 181-192.

[10]Ahmad NSB, Shuib NLM, Surin ESM. Infertility expert system architecture for early diagnosis. *Int J Inform Syst Engin* 2014; **2**(1): 135-140.

[11]Sukar N, Shuib NLM. An expert system framework for infertility in women using web based application. *Int J Inform Syst Engin* 2014; **2**(1): 57-64.

[12]Welling L, Thomson L. *PHP and MySQL web development*. 5th ed. USA: Addison-Wesley Professional; 2016, p. 688.

[13]Akerkar R, Sajja P. *Knowledge–based systems*. Sudbury, Massachusetts, USA: Jones & Bartlett Publishers; 2010, p. 39.

[14]Souza FD. *Development and assessment of two systems for sterility diagnosis*. [Desenvolvimento e avaliação de dois sistemas para o diagnóstico de esterilidade] João Pessoa, PB, Brazil: Universidade Federal da Paraíba; 1997, p. 1-200.

[15]González-Andújar JL. Expert system for pests, diseases and weeds identification in olive crops. *Expert Syst with Appl* 2009; **36**(2): 3278-3283.

[16]Nohria R. Medical expert system - A comprehensive review. *Int J Comp Appl* 2015; **130**(7): 44-50.

[17]Rich E, Knight K, Nair SB. *Artificial intelligence*. 3rd ed. New Delhi: Tata McGraw-Hill Education Pvt. Ltd.; 2008, p. 568.

[18]Inhorn MC, Patrizio P. Infertility around the globe: New thinking on gender, reproductive technologies and global movements in the 21st century. *Hum Reprod Update* 2015; **21**(4): 411-426.

[19]Bieber EJ, Sanfilippo JS, Horowitz IR, Shafi MI. *Clinical gynecology*. 2nd ed. UK: Cambridge University Press; 2015, p. 303.

[20]Farzadi L, Ghasemzadeh A, Bahrami-Asl Z, Shirdel H. Predictors of irrational parenthood cognitions in an Iranian group of infertile women. *PLoS One* 2015; **10**(3): e0070239.

[21]Ombelet W, Cooke I, Dyer S, Serour G, Devroey P. Infertility and the provision of infertility medical services in developing countries. *Hum Reprod Update* 2008; **14**(6): 605-621.

[22]European Society of Human Reproduction and Embryology. *ESHRE monographs*. In: Ombelet W, Devroey P, Gianaroli L, Te Velde E, editors. Oxford University Press; 2008. [Online] Available from: https://doi.org/10.1093/humrep/den176 [Accessed on 18th September 2017].

[23]Ardabily HE, Moghadam ZB, Salsali M, Ramezanzadeh F, Nedjat S. Prevalence and risk factors for domestic violence against infertile women in an Iranian setting. *Int J Gynecol Obstet* 2011; **112**(1): 15-17.

[24]Stamatis DH. *Essential statistical concepts for the quality professional*. Boca Raton, FL, USA: CRC Press; 2012, p. 53.

[25]Fletcher RH, Fletcher SW, Fletcher GS. *Clinical epidemiology: The essentials*. 5th ed. Baltimore-USA: Lippincott Williams & Wilkins; 2012, p. 175-193.