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Using Bayesian networks model predicting pregnancy after psychiatric interventions in infertile couple

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ABSTRACT

Background & Aim: Considering the psychosocial model of diseases, the aim of this study was to evaluate the effect of psychiatric intervention with regard to demographic and marriage characteristics on the pregnancy rate using Bayesian network model in infertile women.

Methods & Materials: In a randomized clinical trial, 638 infertile patients referred to an infertility clinic were evaluated. Among them, 140 couples with different levels of depression in at least one of the spouses were included in this substudy. These couples were divided randomly into two groups. After psychiatric intervention the clinical pregnancy rates of the two groups. The data were divided into two groups: demographic characteristics and marriage specifications, and by drawing Bayesian networks using Grow-Shrink (GS) algorithm, the conditional probability of pregnancy was estimated.

Results: According to the results, Bayesian network model of the GS algorithm was significant (P = 0.548) and given that the fertility in the intervention group who were concurrently treated with antiretroviral treatment, the conditional probability was 38.5%, and this amount in the control group is 3.5% and group who were concurrently treated with induction of ovulation or did not receive any treatment the conditional probability was 72.2% and this amount in the control group is 23.1% comparing the values shows the importance of psychiatric intervention in increasing pregnancy rate.

Conclusion: Results obtained from Bayesian network model are in line with results obtained from logistic model in terms of the significance of the variables with the difference that apart from the graphic structure, Bayesian network model also estimates conditional probabilities. This study shows that psychiatric and psychological treatments play an important role in curing infertility that will increase the chances of pregnancy.

Introduction

Infertility has mental, social, and reproductive consequences. The aim of this study is to evaluate the effect of psychiatric intervention on the pregnancy rate of infertile couples. In an experimental and intervention-control study, 638 infertile patients who were referred to a university infertility clinic were evaluated; 140 couples (280 patients) with depression (from mild to severe) in at least one of the spouses were followed. All couples provided informed consent and were randomly numbered from 1 to 140. Those with even numbers were assigned to the psychological intervention before infertility treatment, and those with odd numbers were assigned to the psychological intervention during infertility treatment. Patients in the experimental group received 6-8 sessions of psychotherapy

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(individually) before beginning infertility treatment and were given Fluoxetine (antidepressant) at 20-60 mg per day during the psychotherapy period. The control group did not receive any intervention. Three questionnaires, the Beck depression inventory, the stress scale (Holmes-Rahe), and a socio-demographic questionnaire, were administered to all patients before and after treatment. The clinical pregnancy rate was compared between the two groups based on sonographic detection of gestational sac 6 weeks after the last menstrual period (1). In both groups, age, education, medical treatment program, length of marriage, and duration of infertility were registered and the separation of these functions into two distinct groups demographic and marriage, by drawing two network effect of this variable on the probability of pregnancy was achieved.

The reasons for choosing Bayesian networks as a vehicle for our ideas are:

1. They are graphical models, capable of displaying relationships clearly and intuitively.
2. They are directional, thus being capable of representing cause-effect relationships.
3. They can handle uncertainty.
4. They handle uncertainty through the established theory of probability.

They can be used to represent indirect in addition to direct causation (2-4).

Methods

***D-separation**:* Bayesian networks encode the dependencies and independencies between variables. Under the causal Markov assumption, each variable in a Bayesian network is independent of its ancestors given the values of its parents. With the causal Markov assumption, we can check some conditional independence in Bayesian networks. For the general, conditional independence in a Bayesian network, Pearl proposed a concept d-separation for the purpose. D-separation is a graphical property of Bayesian networks and has the following implication: If two sets of nodes X and Y are d-separated in Bayesian networks by a third set Z (excluding X and Y), the corresponding variable sets X and Y are independent given the variables in Z. The definition of d-separation is as follows: two sets of nodes X and Y are d-separated in Bayesian networks by a third set Z (excluding X and Y) if and only if every path between X and Y is "blocked," where the term "blocked" means that there is an intermediate variable V (distinct from X and Y) such that:

- The connection through V is "tail-to-tail" or "tail-to-head" and V is instantiated.
- Or, the connection through V is "head-to-head," and neither V nor any of V's descendants have received evidence (3,5).

Markov blanket: It is surprising, however, how little attention it has attracted in the context of Bayesian network structure learning for all its being a fundamental property of a Bayesian network. The definition of a Markov blanket is as follows: for any variable $X \in U$, the Markov blanket BL(X) U is any set of variables such that for any $Y \in U - BL(X) - \{X\}$, $X \perp Y | BL(X)$. In other words, BL(X) completely shields (d-separates) variable *X* from any other variable outside $BL(X) \cup X$. The notion of a minimal Markov blanket, called a Markov boundary, is also introduced in Pearl (2nd Ed., 1997) and its uniqueness shown under certain conditions. The Markov boundary is not unique in certain situations, such as the equality of two variables. In our following discussion, we will assume that the conditions necessary for its existence and uniqueness are satisfied and we will identify the Markov blanket with the Markov boundary, using the notation B(X) for the blanket of variable X from now on. It is illuminating to mention that, in the Bayesian network framework, the Markov blanket of a node X is easily identifiable from the graph: It consists of all parents, children, and parents of children of X (6-9).

Bayesian network structure: Bayesian network structure learning algorithms can be grouped into two categories.

Constraint-based algorithms: These algorithms learn the network structure by analyzing the probabilistic relations entailed by the Markov property of Bayesian networks with conditional independence tests and then constructing a graph which satisfies the corresponding d-separation statements. The resulting models are often interpreted as causal models even when learned from observational data.

Score-based algorithms: These algorithms assign a score to each candidate Bayesian network and try to maximize it with some heuristic search algorithm. Greedy search algorithms (such as hill-climbing or tabu search) are a common choice, but almost any kind of search procedure can be used.

Constraint-based algorithms are all based on the inductive causation algorithm by Verma and, which provides a theoretical framework for learning the structure causal models. It can be summarized in three steps:

1. First, the skeleton of the network (the undirected graph underlying the network structure) is learned. Since an exhaustive search is computationally unfeasible for all but the most simple datasets, all learning algorithms use some kind of optimization such as restricting the search to the Markov blanket of each node (which includes the parents, the children, and all the nodes that share a child with that particular node).
2. Set all direction of the arcs that are part of a v-structure.
3. Set the directions of the other arcs as needed to satisfy the acyclicity constraint.

Score-based algorithms, on the other hand, are simply applications of various general purpose heuristic search algorithms, such as hill-climbing, tabu search, simulated annealing, and various genetic algorithms. The score function is usually score-equivalent so that networks that define the same probability distribution are assigned the same score. In this study, we used constraint-based algorithms [Grow-Shrink (GS) algorithm] (7).

Bayesian network local pdfs: The second component of a BN is a set of local conditional probability distributions. Together with the graph structure, they are sufficient to represent the joint probability distribution of the domain. More concretely, in other words, the joint pdf of the domain can be factorized into smaller, local pdfs each involving a node and its parents only (8). Viewed in this way, the local pdfs provide the quantitative probabilities that, when multiplied together in the fashion prescribed by the qualitative independencies that are implied by the structure of the BN, are sufficient to reconstruct the joint pdf of the domain. Any probability distribution family can be used for the local pdfs. The independencies displayed in the structure of the BN hold true for every member of the family that is consistent with the structure. In other words, they are true for any choice of parameters for the local pdfs. In practice, when a variable and its parent in the graph are discrete, these local pdfs are frequently represented by a multinomial distribution. When they are continuous, mixtures of Gaussians and artificial neural networks have been used in practice.

The mathematical form of a Bayesian network includes couples BN = (S, P) and S = (N, A) that N is number of nodes, and A is number of edges. If X_1, X_2, X_3, …, X_n are random variables, acyclic graph with N nodes that node of j ($1 \leq j \leq n$) is for X_j, is Bayesian network if:

$$P(X_1, X_2, X_3, \dots, X_n) = \prod_{j=1}^{n} P\left(X_j \middle| \text{parents}(X_j)\right)$$

The GS Markov Blanket Algorithm

1. $S \leftarrow 0$
2. While $\exists\ Y \in U\text{-}\{X\}$ such that $Y \not\perp X |\ S$, do $S \leftarrow S \cup \{Y\}$ (Growing phase)
3. While $\exists\ Y \in S$ such that $Y \perp X |\ S\text{-}\{Y\}$, do $S \leftarrow S\text{-}\{Y\}$ (Shrinking phase)
4. $B(X) \leftarrow S$

(Figure 1)

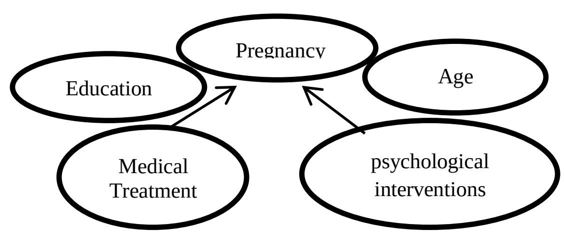

Figure 1. Bayesian network model obtained from Grow-Shrink algorithm for demographic profile data

In figure 1, we present an algorithm, called GS, for the recovery of the Markov blanket of X based on pairwise independence tests. It consists of two phases, a growing and a shrinking one, hence its name. Starting from an empty set S, the growing phase adds variables to S as long as they are dependent on X given the current contents of S. The idea behind this is simple: as long as the Markov blanket property of X is violated (i.e., there exists a variable in U that is dependent on X given the current S), we add it to the current set S until there are no more such variables. In this process, however, there may be some variables that were added to S that were really outside the blanket. Such variables are those that have been rendered independent from X at a later point when “intermediate” (d-separating) nodes of the underlying Bayesian net were added to S. This observation motivates the shrinking phase, which identifies and removes these variables. In general, this algorithm has the following steps to build a Bayesian network:

1. (Compute Markov Blankets)

For all X Є U, compute the Markov blanket B(X)

2. (Compute Graph Structure)

For all X Є U and Y Є B(X) determine Y to be a direct neighbor of X if X and Y are dependent given S for all T ⊇ S where T is the smaller of B(X)-{Y} and B(Y)-{X}.

3. (Orient Edges)

For all X Є U and Y Є N(X) orient Y → X if there exists a variable Z Є N(X) – N(Y) – {Y} such that Y and Z are dependent given S∪{X} for all T ⊇ S where T is smaller of B(Z) – {X,Y} and B(Y) – {X, Z}.

4. (Remove Cycles)

Do the following while there exist cycles in the graph:

- Compute the set of edges C={X → Y} such that X → Y is part of a cycle.
- Remove from the current graph the edge in C that is part of the greatest number of cycles, and put it in R.

5. (Reverse Edges)

Insert each edge from R in the graph in reverse order of removal in Step 4, reversed.

6. (Propagate Directions)

For all X Є U and Y Є N(X) such that neither X → Y nor Y→X executes the following rule until it no longer applies: If there exists a directed path from X to Y, orient X → Y.

Finally, using the log-linear model, conditional probability, were estimated by Bayesian network structure of GS algorithm. The first step in fitting Bayesian network structure by linear logarithmic model is regarding the relationship between variables and build models based on the interactions between variables can be defined by the edges (2).

The software used in this study: HUGIN, R, SPSS (version 17, SPSS Inc., Chicago, IL).

Finding: The age range of women under study was 19-41 years with a mean of 26.3, and a standard deviation of 4.4 and duration of marriage and infertility was 1-20 years with a mean of 6.4 and a standard deviation of 4. According to table 1, investigating the ratio of pregnancy outcome in patients under intervention group showed that 33 cases (47.1%) in control group showed 5 cases (7.1%) and this difference is statistically significant.

Table 1. Demographic characteristics of subjects: Results

Variable	Group	Intervention	Control
		Frequency (%)	Frequency (%)
Pregnancy	Yes	33 (47.1)	5 (7.1)
	No	37 (52.9)	92 (9)
Medical treatment	No, induction of ovulation	18 (25.7)	13 (18.6)
	ART	52 (74.3)	57 (81.4)
Age	≤ 25	34 (48.6)	34 (48.6)
	25-35	34 (48.6)	34 (48.6)
	≥ 36	2 (2.8)	2 (2.8)
Education	Primary	19 (27.1)	26 (37.1)
	Secondary	18 (25.7)	19 (27.1)
	Diploma	26 (37.1)	23 (32.9)
	upper diploma	7 (10)	2 (2.9)
Duration of marriage	1-5	72 (51.4)	69 (49.3)
	6-10	50 (35.7)	50 (35.7)
	11-15	14 (10)	11 (7.9)
	16-20	4 (2.9)	10 (7.2)
Duration of infertility	1-5	86 (61.4)	78 (55.7)
	6-10	38 (27.1)	44 (31.4)
	11-15	14 (10)	10 (7.1)
	16-20	2 (1.4)	8 (5.7)

ART: Antiretroviral treatment

Investigating the ratio of pregnancy outcome in patients in intervention group under no, induction of ovulation medical treatment (25.7%) and under antiretroviral treatment (ART) (74.3%). Investigating the ratio of pregnancy outcome in patients in intervention group and age ≤ 25, (48.6%), 25-35 (48.6%), and ≥ 36 (2.8%). Investigating the ratio of pregnancy outcome in patients in intervention group and primary education (27.1%), secondary education (25.7%), diploma (37.1%), and upper diploma (10%). Investigating the ratio of pregnancy outcome in patients in intervention group and duration of marriage 1-5 (51.4%), 6-10 (35.7%), 11-15 (10%), and 16-20 (2.9%). Investigating the ratio of pregnancy outcome in patients in intervention group and duration of infertility 1-5 (61.4%), 6-10 (27.1%), 11-15 (10%), and 16-20 (1.4%).

According to the definition of Bayesian networks and figure 1, treatment programs and psychiatric interventions cause pregnancy and any changes in the probability of pregnancy will take place under these two conditions. Education and age groups had no effect on pregnancy level. These results are equal to the logistic model in which the treatment program and psychiatric intervention are significant with P values of < 0.001 and equal to 0.002 and education and age group are not significant with P values of 0.900 and 0.400, respectively.

According to the definition of Bayesian networks and figure 2, treatment programs and psychiatric interventions cause pregnancy and any changes in the probability of pregnancy will take place under these two conditions. Marriage duration and infertility duration had no effect over pregnancy level, which is significant in logistic model of the treatment program and psychiatric intervention with P values of 0 and 0.002, while marriage duration with a P value of 0.800 is not included in the model and infertility duration with a P value of 0.500 is not significant.

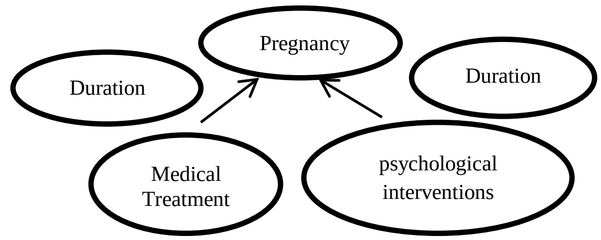

Figure 2. Bayesian network model obtained from Grow-Shrink algorithm for marriage profile data

If we put X for the dependent variable "pregnancy," Y for psychiatric intervention and Z for a treatment program, the formula for the log-linear model of Bayesian network obtained from GS will be as follows (10):

$$= \lambda + \lambda_i^x + \lambda_{ij}^{xy} + \lambda_{ik}^{xz} \mathrm{Log}\, \mu_{ijk}$$

LR index and chi-square statistics with values of 0.36 and 0.36 and degree of freedom of 1 were used for goodness of fit test. P value of the two models that equals 0.540 shows the Bayesian network model is acceptable. The values of Pearson's chi-square and the likelihood ratio generally confirm appropriateness of the model, while they do not investigate each and every cell. The rest of the model is used to study every cell in the 3D table. By the increase in the remaining in table cells, it can be concluded that the model has not been appropriate to describe those table cells. To make sure that the investigation of the remaining has been correct, adjusted remaining obtained from dividing the remaining by the standard error of the estimate is used which also considers the sample size.

Observed and expected values are shown in table 2.

Table 2. Observed and expected values: Result of Bayesian network

Psychological interventions	Medical treatment	Result of pregnancy	Observed Frequency (%)	Expected Frequency (%)	Residual	Adjusted residual
Intervention	ART	Positive	20 (38.5)	19.47 (37.4)	0.529	0.601
		Negative	32 (61.5)	32.52 (62.6)	-0.529	-0.602
	NO, induction of ovulation	Positive	13 (72.2)	13.50 (75.2)	-0.529	-0.602
		Negative	5 (27.8)	4.47 (24.8)	0.529	0.601
Control	ART	Positive	2 (3.5)	2.52 (4.4)	-0.529	-0.601
		Negative	55 (96.5)	54.47 (95.6)	0.529	0.602
	NO, induction of ovulation	Positive	3 (23.1)	2.47 (19)	0.529	0.601
		Negative	10 (76.9)	10.52 (81)	-0.529	-0.602

Table 3. Estimate of parameters: Result of Bayesian network

Parameter	Estimate	Standard error	Z	P value
Constant	3.48	-	-	-
ART and psychological interventions				
Constant	3.99	-	-	-
ART and control				
Constant	1.49	-	-	-
No, induction of ovulation and psychological interventions				
Constant	2.35	-	-	-
No, induction of ovulation and control				
Pregnancy	−1.44	0.55	−2.61	0.009
Pregnancy and ART	−1.62	0.51	−3.12	0.002
Pregnancy and psychological interventions	2.55	0.55	4.62	-

According to table 2, considering the comparison of the observed and expected values, the closeness of these values can be found. According to the obtained results from Bayesian network model, it is concluded that the probability of pregnancy in patients under psychiatric intervention and ART treatment program is 38.5% and this probability is 72.2% in people receiving “induction of ovulation” program or no treatment. The probability of pregnancy in people who receive ART treatment program in the control group is 3.5%, and this is 23.1% in people who receive “induction of ovulation” treatment program or no treatment. Investigating and comparing the adjusted residuals, it is concluded that the model has estimated the conditional probabilities with high accuracy. In general, women who receive an induction of ovulation treatment program or no treatments become pregnant more in both control and intervention groups compared to the other treatment group.

According to table 3, the effect of being pregnant is less than the source group and equals -1.44, and its effect is significant in table cells with a P value of 0.009. Mutual effect of ART treatment program and those who got pregnant was estimated to be -1.62, which is less than the source group with ART treatment program and those who did not become pregnant. This shows the low effect of this group compared to the reference group in the estimation of the expected values in the table. Considering the $P = 0.002$, the effect of this mutual effect is statistically significant. Estimation of the mutual effect of pregnancy parameter and those who received psychiatric intervention is 2.55 which is statistically significant with an eye on the $P < 0.001$ of the effect of this mutual effect in the estimation of the 3D table cells. Results of the effect of different variables in the presence of psychiatric intervention on pregnancy in Bayesian network model are in line with results obtained from logistic model with the difference that apart from the graphic structure, the Bayesian network model also estimates conditional probabilities. Considering the values of the remaining and adjusted remaining, Bayesian network model has high accuracy in estimation of conditional probabilities of pregnancy.

Results

Research results show that people with no medical treatments or those who received “induction of ovulation” medical treatment simultaneous with psychiatric intervention had higher probability of pregnancy compared to those who received ART treatments. Considering the small sample size in different treatment groups that led us categorizes different treatment groups in two, which is one of the limitations of this study, it is recommended to evaluate the psychiatric intervention effect in different treatment groups by increasing the sample size and analyzing them psychologically. This study shows that psychiatric and psychological treatments play an important and crucial role in curing infertility that increases the chances of becoming pregnant. According to the results obtained from this study and other studies, psychiatric, and psychological treatments should accompany medical treatments of infertility which will, in turn, increase pregnancy.

Discussion

Cwikel et al. (11) reported that psychological factors such as stress and anxiety lead to changes in the heartbeat and cortisol hormone, while some studies do not confirm the relationship between stress and infertility (12,13). Stress can be reduced through cognitive-behavior therapies (relaxation), especially at *in vitro* fertilization (IVF)-EF. Therefore, the probability of pregnancy can increase through these therapies (14,15). In addition, other reports indicate that cognitive-behavior therapies and psychotherapy at the time of treatment, diagnosis and tests of pregnancy will lead to positive IVF, especially before pregnancy and psychotherapies increase the probability of pregnancy even after 6 months of follow-ups (16,17). However, Yong et al. (18) do not confirm this relationship. They believe consultancy is not effective for those exposed to the first IVF cycle. However, the number of these studies is few and limited.

Research results seem to be consistent with findings of other studies. Therefore, stress can be a significant factor in infertility and reduction of stress can lead to an increase in the probability of pregnancy in infertile couples. The increase in the probability of pregnancy in the experimental group shows the effect of medicinal and psychiatric treatments.

Using Bayesian categories and examining the characteristics of the fetuses in 2008, Morales et al. (19) estimated their reproduction ability. Using ROC curve analysis, Morales et al. (19) proved that the categorization used in this study is a strong and appropriate method. In the following, Corani et al. (20) predicted the output of IVF by the use of Bayesian method. Finally, they investigated the effectiveness of the proposed model by comparing the predicted results with actual data. Kim and Jung (21) discussed the superiority of Bayesian network method over the simple Bayesian method. They applied exploration tactics and simple Bayesian and Bayesian network methods on infertility data and concluded that Bayesian network is very accurate. In the paper that Bozgurt published in 2011, they used Bayesian networks and logistic regression methods to predict prostate cancer and by comparing the area beneath ROC curve in the two models, they concluded that Bayesian networks are a little more accurate (22). The fact that most of the articles which have used Bayesian networks for categorization or prediction of infertility have reached conclusions consistent with our findings indicates the high accuracy of this model.

Conclusion

Results of the effect of different variables on fertility in the presence of psychiatric intervention in Bayesian network model are in line with results of logistic model with the difference that Bayesian network model meets conditional probabilities besides the graphic structures. According to the values of remainders and adjusted remainders, Bayesian network model is more accurate in estimating conditional probabilities. Research results show that individuals with no medical plans or those receiving psychiatric intervention simultaneous with induction of ovulation treatment are more probable to get pregnant than those receiving ART treatments. Considering the few number of samples in different experimental groups which led to categorization of them in two groups – one of the limitations of the study –, it is suggested that each of the experimental groups be examined under psychiatric interventions when the number of the samples is increased, and results are psychologically analyzed. This study shows that psychiatric and psychological treatments play a crucial role in curing infertility, which leads to an increase in successful pregnancy. According to this research results and other studies, psychiatric and psychological treatments should accompany medical treatments of infertility which can result in an increase in pregnancy.

Conflict of Interests

Authors have no conflict of interests.

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