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FACTORS AFFECTING THE OUTCOME OF IN VITRO FERTILIZATION (IVF)

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Abstract

The high prevalence of infertility motivated researchers to find a solution, henceforth In Vitro Fertilization was invented. Factors that affect the outcome of IVF may include sperm analysis, maternal Body Mass Index (BMI), maternal smoking habits, endometriosis, and maternal age. However, there are ongoing debates about the role of said factors regarding the outcome of IVF. The objective of this research is to analyze those factors. This research is a Case-Control study with an analytical observational design. Data were retrieved from patients' medical records undergoing IVF in Graha Amerta Fertility Clinic from January 2019-October 2020. First, the Chi-Square Test revealed sperm abnormality (p=0.212), Maternal BMI (p=0.427), endometriosis (p=0.067), meaning there was no connection with the outcome of IVF. Simultaneously, maternal age (p=0.037) showed a connection with the outcome of IVF. From the Binary Logistic Regression Test, maternal age 36-40 years old (p=0.044) affects the outcome of IVF significantly. Concurrently maternal BMI, endometriosis, and sperm abnormality have p value>0.05 meaning it is insignificant to the outcome of IVF. This research concluded that sperm abnormality, maternal BMI, and endometriosis do not affect the outcome of IVF. There was no data about maternal smoking habits. Whilst maternal age affects the outcome of IVF. Conclusion: This research concluded that sperm abnormality, maternal BMI, and endometriosis do not affect the outcome of IVF. There was no data about maternal smoking habits. Whilst maternal age affects the outcome of IVF.

Keywords: *in vitro fertilization; good health and well-being; infertility*

Introduction

It is estimated there are 15% of reproductive-aged couples in the world who experienced difficulty when it comes to having children (1). Infertility and its high prevalence have been the dread of partners around the globe since the dawn of time. Infertility can be due to a myriad of causes, be it from the maternal or paternal side. However, the general public has long believed that infertility was caused solely by women, causing an unbalanced social burden for women. It is contrary to evidence that found men have a 20-30% chance of causing infertility, while women contributed to 50% chance of causing infertility, combined factors are 20-30% (2). Infertility in

women is due to ovulatory disruption, tubal and pelvic disorder, and uterine disorder. On top of that, the most common causes are ovulatory disruption and tubal disorders (3). Whereas infertility in men is caused by semen quality, endocrine disruption, erectile dysfunction, ejaculation disorder, etc (4). To note, the most frequent causes of infertility for men lies in semen quality, azoospermia, and faulty intercourse method (4). Along with the development of technology, In Vitro Fertilization (IVF) was deemed to be a suitable solution for infertility. The IVF procedure consists of three crucial steps; ovulation induction, oocyte fertilization, and embryo development after being transfered to the uterus (5). Although it was considered a breakthrough, IVF has a high percentage of failure. It was due to clinical variation in each individual and couples who undergo IVF. If pregnancy does not happen, then it is considered a cycle failure. Pregnancy itself is affirmed by measuring serum Beta-hCG level 15 days after ovum retrieval. A chemical pregnancy is confirmed when serum Beta-hCG levels are higher than 25 mIU/mL (6). There are a multitude of factors that may affect the outcome of IVF. Aside from a disturbance during the processes of IVF, there is the role of clinical variations that includes maternal Body Mass Index (BMI), maternal smoking habits, endometriosis, maternal age, and paternal sperm abnormality. Debates are still ongoing on whether these factors affect the outcome of IVF. Weighing the emotional and financial burden of a cycle cancellation for the couples, the urgency of analyzing factors that affect the outcome of IVF is imperative.

Methods

1. Study Design

This research is an analytical observational study. The purpose for using analytical design is to uncover why and how a phenomenon occurs through a statistical analysis, such as risk factor and its effect, and can be used to determine the weight of a risk factor's contribution towards its effect. This research's design is a Case Control study initiated between January 1, 2019, and October 31, 2020 at Graha Amerta Fertility Clinic RSUD Dr, Soetomo and was approved by the RSUD Dr. Soetomo Ethical Committee. The sampling technique used in this research is total sampling. For sperm analyses, patients were grouped according to the World Health Organization (WHO) Semen Parameters Reference (7). Normal sperm analysis was defined as patients who have none or one abnormal semen parameter, abnormal sperm analysis has two or more abnormal semen parameters. The semen parameters are categorized as asthenozoospermia if sperm concentration is <15x106/mL, oligozoospermia if sperm motility is <40%, and teratozoospermia if sperm morphology is <4%. For Body Mass Index (BMI), patients were grouped according to the World Health Organization (WHO) BMI Classification (8). Underweight patients were defined as those having a BMI of <18.5 kg/m2, normal-weight have a BMI of 18.5-24.9 kg/m2, pre-obese have a BMI of 25-29.9 kg/m2, and obese patients have a BMI of ≥30 kg/m2. For maternal smoking habits, patients were grouped as non-smoker and smoker and/or passive smoker. For endometriosis,

patients were also divided into two groups, being history of endometriosis and none. For maternal age, patients were divided into three age groups, 25-35 years old, 36-40 years old, and >40 years old. All data were collected from medical records at Graha Amerta Fertility Clinic.

2. Patients

   The population for this study was 256 patients. Cases were patients who underwent IVF procedure at Graha Amerta Fertility Clinic with a time period of January 1, 2019-October 31, 2020. This study required medical records to be complete and within the time period. We excluded medical records that are incomplete or missing and patients with drop out status. From the initial total population of 256 patients, after thorough screening according to the inclusion and exclusion criteria, a sample of 179 patients were obtained. There were 58 incomplete medical records, and 19 patients with dropout status. Datas that were collected from medical records are as follows, sperm abnormality, maternal BMI, maternal smoking habits, endometriosis, and maternal age. However, during data collection we did not find any datas regarding maternal smoking habits. Afterwards, data were categorized into two, successful IVF procedure and failed IVF procedure.

3. Outcome

   The main outcome of the study was a successful IVF procedure indicated by chemical and clinical pregnancy. This was achieved by calculating serum Beta-hCG levels at 15 days after ovum retrieval and through imaging with ultrasonography (USG). Chemical pregnancy is defined when Beta-hCG levels are >25mIU/mL and clinical pregnancy is defined when a gestational sac is found during week 4-5 of pregnancy using USG (6).

4. Statistical Analyses

   Outcome measures between groups were distributed and then compared using univariate analysis and bivariate analysis that is Chi-Square Test and Partial Test with Binary Logistic Regression Method. Where $p<0.05$ was considered statistically significant

Result

Research on factors that affect the outcome of In Vitro Fertilization (IVF) at Graha Amerta Fertility Clinic of Dr. Soetomo Hospital Surabaya was conducted in February 2021. The data taken in the form of secondary data is the medical record of patients undergoing IVF procedure at Graha Amerta Fertility Clinic of Dr. Soetomo Hospital Surabaya period January 2019-October 2020. The population was 256 couples. After adjusting for the criteria of inclusion and exclusion, a sample of 179 couples was obtained. The number of incomplete medical records is 58 and patients with Drop Out status amount to 19. From the sample obtained, there were 68 couples or 38% who successfully underwent IVF and achieved pregnancy, while there were 111 couples or 62% who failed to undergo IVF and did not achieve pregnancy. The data taken from medical records in the form of sperm abnormalities, BMI of female patients, the habit of

female patients smoking, endometriosis disease in female patients, and the age of female patients. However, medical records of data on the smoking habits of female patients were not recorded. The data that has been obtained will be grouped into two categories, namely IVF successful and IVF failed. From the sample obtained, there were 68 couples or 38% who successfully underwent IVF and achieved pregnancy, while there were 111 couples or 62% who failed to undergo IVF and did not achieve pregnancy. The data taken from medical records in the form of sperm abnormalities, BMI of female patients, the habit of female patients smoking, endometriosis disease in female patients, and the age of female patients. However, medical records of data on the smoking habits of female patients were not recorded. The data that has been obtained will be grouped into two categories, namely IVF successful and IVF failed. From the sample obtained, there were 68 couples or 38% who successfully underwent IVF and achieved pregnancy, while there were 111 couples or 62% who failed to undergo IVF and did not achieve pregnancy. The data taken from medical records in the form of sperm abnormalities, BMI of female patients, the habit of female patients smoking, endometriosis disease in female patients, and the age of female patients. However, medical records of data on the smoking habits of female patients were not recorded. The data that has been obtained will be grouped into two categories, namely IVF successful and IVF failed. The results of the analysis on the influence between sperm abnormalities, Body Mass Index (BMI) of female patients, endometriosis disease of female patients and the age of female patients against the outcome of IVF at Graha Amerta Fertility Clinic dr. Soetomo Hospital Surabaya Period 2019-2020 using Binary Logistic Regression method can be explained as follows.

A. Characteristics of Research Data

The proportion of each category on variables thought to affect IVF output can be shown in Table 5.1 as follows.

Table 1
Proportion of Research Data

Variable	n	Marginal Percentage
Sperm Abnormalities		
Normal	130	72,6%
Abnormal	49	27,4%
Women's Body Mass Index		
Underweight	10	5,6%
Normal	105	58,7%
Pre-Obesity	50	27,9%
Obesity	14	7,8%
Penyakit Endometriosis		
Existing	27	15,1%
None	152	84,9%
Women's Age		
25-35 Years Old	131	73,2%
36-40 Years Old	36	20,1%
>40 Years Old	12	6,7%

IVF		
Successful cycle	68	38%
Failed cycle	111	62%

Table 5.1 shows the number of patient samples in this study there were 179 patients at Graha Amerta Fertility Clinic of Dr. Soetomo Hospital Surabaya for the period 2019-2020. The percentage of normal sperm abnormalities is 72.6% and abnormal is 27.4%, meaning most patients have normal sperm analysis results. The percentage of body mass index (BMI) of women consists of underweight as much as 5.6%, normal 58.7%, pre-obesity 27.9% and obesity 7.8%. This suggests that the majority of female patients have normal BMI and some are pre-obese. The percentage of endometriosis in female patients is 15.1% and the absence of endometriosis in female patients is 84.9%. This suggests that the majority of female patients do not have endometriosis. The age of female patients in this study was divided into 3 with the following percentage, 25-35 years by 73.2%, 36-40 years by 20.1% and >40 years by 6.7% so that the majority of patients aged 25-35 years. Based on the exterior of IVF, it is known that 38% of patients with IVF status succeeded and 62% of IVF patients failed.

B. Relationship Analysis

Characteristics of the IVF outcome data based on sperm abnormalities, female BMI, endometriosis disease and the age of women using cross tabulation are shown in Table 5.2 as follows.

Tabel 2
Cross Tabulation

Variable	IVF exterior				P
	IVF succeeds		IVF Failed		
	n	%	n	%	
Sperm Abnormalities					
Normal	53	40,8	77	59,2	0,212
Abnormal	15	30,6	34	69,4	
Women's Body Mass Index					
Underweight	5	50,0	5	50,0	
Normal	35	33,3	70	66,7	0,427
Pre-Obesity	21	42,0	29	58,0	
Obesity	7	50,0	7	50,0	
Penyakit Endometriosis					
Existing	6	22,2	21	77,8	0,067
None	62	40,8	90	59,2	
Women's Age					
25-35 years old	57	43,5	74	56,5	**0,037**
36-40 years old	9	25,0	27	75,0	
>40 years old	2	16,7	10	83,3	

Table 5.2 shows patients with normal sperm who had IVF succeeded by 40.8% and IVF failed by 59.2%. Patients with abnormal sperm who had IVF succeeded by

30.6% and IVF failed by 69.4%. This indicates that patients with abnormal sperm experience more IVF failure.

Patients with an underweight BMI who experience successful IVF and IVF fail are the same, both at 50%. Patients with normal BMI who experienced IVF succeeded by 33.3% and IVF failed by 66.7%. Patients with pre-obese BMI who had IVF succeeded by 42% and IVF failed by 58%. Patients with an obese BMI who had a successful IVF cycle, and a failed IVF cycle were the same, at 50% each. This suggests that women with normal BMI experience more IVF failure.

Patients with endometriosis who successfully underwent IVF procedure by 22.2% and failed to undergo IVF procedure by 77.8%. Patients without endometriosis who had IVF succeeded by 40.8% and IVF failed by 59.2%. This suggests that patients with endometriosis are more concerned about failing to undergo IVF.

Patients aged 25-35 years who experienced IVF succeeded by 43.5% and IVF failed by 56.5%. Patients aged 36-40 years who experience IVF succeed 25% and IVF fail 75%. Patients aged >40 who had IVF managed 16.7% and IVF failed 83.3%. This suggests that more >40-year-old patients who experience IVF fail.

Analysis of relationships using the Chi Square-Test between each independent variable and the dependent variable, i.e. IVF outcome. The analysis used is the Chi Square value with a confidence interval of 95%. If between an independent and dependent variable produces a p value < 0.05 then there is a relationship between the independent variable and the IVF outcome.

Table 5.2 shows that the results of statistical analysis on variable sperm abnormalities (p=0.212), female BMI (p=0.427), endometriosis disease (p-0.067) have a p>0.05 value which means there is no relationship between sperm abnormalities, female BMI, endometriosis disease toward IVF outcome. While the age of the woman (p = 0.037) has a value of p < 0.05 which means there is a relationship between the age of the woman and the outcome of IVF.

C. Analysis of Factors Affecting IVF Outcome (Partial Test)

The influence between independent variables on dependent variables i.e. the outcome ity of IVF procedures can be tested using the Binary Logistic Regression Method with a confidence interval of 95%. If an independent variable produces a p value < 0.05 then the variable becomes a significant factor in the IVF output. Partial Test Results are shown in Table 5.3.

Tabel 3
Partial Test

Variable	P_{value}	OR	OR (CI 95%)	Conclusion
Sperm Abnormalities				
Sperm Abnormalities (Abnormal)	0,157	1,699	0,815-3,542	Insignificant
Female BMI				
Female BMI (Underweight)	0,297	0,486	0,125-1,889	Insignificant

Female BMI (Pre-Obesity)	0,407	0,735	0,355-1,521	Insignificant
Female BMI (Obesity)	0,365	0,582	0,181-1,875	Insignificant
Penyakit Endometriosis				
Endometriosis (Existing)	0,052	2,674	0,991-7,215	Insignificant
Women's Age				
Women's Age (36-40 Years Old)	0,044	2,397	1,025-5,605	Significant
Women's Age (> 40 Years Old)	0,053	4,827	0,980-23,777	Insignificant

Note: The first category is used as a reference category

Table 5.3 shows the results of statistical analysis using partial tests (testing each variable independent of a dependent variable produces a diverse p value for each category on each variable. Variables that have a significant effect on the outcome of IVF is the age of women 36-40 years p (0.044) < p(0.05). This means that the age of women has a significant role in the outcome of IVF. While variable sperm abnormalities, female BMI and endometriosis have a p value of > 0.05 is not significant to the outcome of IVF.

Odds Ratio (OR) analysis is a measure of the relationship of exposure or risk factors to the occurrence of certain results, this is calculated from the incidence of disease in the group exposed to risk factors compared to the incidence of disease in the group that is not exposed to risk factors. Odds Ratio analysis is used to determine the tendency of certain categories to the outcome of IVF procedures. Sperm abnormalities (abnormal) result in an OR value of 1,699 (0.815-3,542) compared to someone who has normal sperm.

A woman's BMI (underweight) produces an OR value of 0.486 (0.125-1.889) compared to someone with a Normal BMI. A woman's BMI (Pre-Obesity) produced an OR value of 0.735 (0.355-1.521) compared to someone with a Normal BMI. A woman's BMI (Obesity) produced an OR value of 0.582 (0.181-1,875) compared to someone with a Normal BMI. This shows that normal female BMI has the highest OR number of all BMI groups.

Endometriosis (Existing) produced an OR value of 2,674 (0.991-7,215) compared to someone who did not have endometriosis.

Women (36-40 years old) produce an OR score of 2,397 (1,025-5,605) compared to someone aged 25-35 years. A woman's age (>40 years) produces an OR score of 4,827 (0.980-23,777) compared to someone aged 25-35 years. This means that women with >40 years of age have the highest OR number of all age groups.

Discussion

1. Sperm Abnormality

Our data demonstrates that sperm abnormality does not have a relationship with the outcome of IVF procedure, this was shown through the p value of 0.212 from the Chi-Square test. From the Binary Logistic Regression we obtained a p value of 0.157, meaning it does not have any significant effect on the outcome of IVF procedure. The Odds Ratio was 1.699 (0.815-3.524) which means there is a 1.699

higher chance of IVF failure in patients with sperm abnormality than patients with a normal sperm analysis. The abnormality that is studied in this research is when there are ≥2 abnormal parameters in the analysis result. We hypothesize that sperm abnormality affects the outcome of IVF. However, from here we can see that both statistical analyses are in accordance, sperm abnormality is not related to and does not affect the outcome of IVF. This finding is aligned with other studies that stated sperm morphology does not affect the outcome of IVF, and sperm concentration does not affect the outcome of IVF, this can be due to the ability of certain cell, including cumulus, oolemma, or zona pellucida to do natural selection on which spermatozoo to fertilize the egg. However this finding is not aligned with some studies, where the fertilization rate is good in good sperm motility (>70%) and moderate (40-70%) but not in poor motility (<40%). It should be taken into consideration that sperm analysis parameters can vary significantly between individuals and between samples from each individual. The difference can be due to procedures on patients with abnormal sperm analysis, such as Intracytoplasmic Sperm Injection that might alter the outcome of IVF. There is also the role of the IVF process that is not studied in this research.

2. Maternal Body Mass Index (BMI)

The Chi-Square test showed the p value of maternal BMI is 0.427, meaning there is no relationship between maternal BMI and IVF outcome. Data from the Binary Logistic Regression also showed a p value of 0.486 for underweight, 0.735 for pre-obese, and 0.582 for obese. This means there are no significant effects on the outcome of IVF procedure. The OR for underweight is 0.486 (0.125-1.889), meaning the risk of IVF failure for underweight BMI are 0.486 times lower than normal BMI. For pre-obese, the OR is 0.735 (0.355-1.521) which means there is a 0.735 lower chance of IVF failure than normal BMI. And the OR for obese BMI is 0.582 (0.181-1.875), meaning the risk for IVF failure is 0.582 times lower than normal BMI. This shows that normal BMI have the highest risk of IVF failure than other categories, and what follows is pre-obese, obese, and underweight. We initially hypothesize that maternal BMI affects IVF outcome. From this finding, we infer that maternal BMI is not related to and does not affect the outcome of IVF. This is inconsistent with other findings, that women who falls in the obese category have a negative effect on conception and implantation through various cumulative degeneration processes like ovulation, oocyte maturation, development of endometrium, uterine receptivity, and an increase of conception time and spontaneous abortion. It was established that in pre-obese and obese BMI, the ovarian response is lower than in normal BMI who received the same stimulation. The same was found in another study which stated BMI has a significant effect on IVF outcome with a p value <0.001, and women with pre-obese BMI and obese have a poor IVF outcome rather than normal BMI. In the same study, pre-obese women were found to have a higher likelihood of cycle cancellation, whereas pre-obese and underweight BMI have lesser embryo. A study also found a decline in blastocyst formation rate in pre-obese and obese BMI, this

leads to an increased chance of embryonic arrest and causing IVF failure. The different findings can be due to a limited sample size, and the assumption of the best quality oocyte were used for fertilization in each BMI category. There are other factors that are not studied including Polycistic Ovarian Syndrome (PCOS) and the role of IVF processes, including the skills of experts in the laboratory and technology used.

3. Maternal Smoking Habits

We were unable to obtain data regarding maternal smoking habits in the patients medical records at Graha Amerta Fertility Clinic. Despite that, there are some findings that should be taken into consideration. Maternal smoking habit leads to a significant increase of serum FSH and decrease of total Antral Follicle Count (AFC) than women who do not smoke. From this, we can infer that smoking habit affects ovarian reserve and IVF outcome. Other than that, smoking also shortens the transition toward menopause and causes early menopause about 1-1.5 years sooner. This is aligned with another study which stated smoking negatively affects IVF outcome, that includes a decrease in amount and quality of oocyte, implantation rate, clinical pregnancy rate, and live birth rate. It is also shown that clinical pregnancy and live birth failure in smokers are 1.5 times higher, while the risk of spontaneous abortion is twice higher, and the risk of ectopic pregnancy is >15 times higher than non-smokers. However, there are some studies that showed the opposite. There are 21.4% of women with cigarette exposure in the population and no significant effect toward IVF outcome were found. It was found there are an increase of oocyte quality that is inversely proportional with smoking habit. The same was found in a study that stated there are no significant differences in oocyte quality, fertilization rate, embryo development rate, and pregnancy rate between smokers and non-smokers. This difference can be due to the assumption of the best quality oocyte were used for fertilization in both smokers and non-smokers. Hence, regarding the effect of maternal smoking habits on the outcome of IVF should be further studied.

4. Endometriosis

From the Chi-Square test, we obtained the p value 0.067 for endometriosis, meaning there are no relationship between endometriosis and IVF outcome. We also obtained the p value 0.052 of endometriosis from the Binary Logistic Regression test, this means there are no significant effect of endometriosis towards IVF outcome. The OR value for endometriosis is 2.674 (0.991-7.215), meaning women with endometriosis have a 2.674 times higher risk of IVF failure. Both statistical analysis are in line, endometriosis is not related to and does not affect the outcome of IVF. This is similar with findings from other studies, endometriosis is closely related to a decrease in live birth rate than other infertility diagnosis, in particular with tubal factors. Albeit, we must highlight the fact that both the relationship and effect of endometriosis on IVF outcome is clouded with the presence of other infertility diagnosis. In the previous study, the majority of participants with endometriosis have at least one other infertility diagnosis, which complicates the assessment of

endometriosis' impact on IVF outcome. In another study, it was stated that endometriosis does not affect IVF outcome, with the exception of participants with significant Diminished Ovarian Reserve (DOR) and needs aggressive stimulation that can affect the amount of oocyte and embryo. However, in another study, endometriosis showed a negative impact on IVF, this can be inferred from the total of clinical pregnancy per OPU cycle and by using AFC as an independent predictor. The negative impact mentioned was mainly caused by Poor Ovarian Reserve (POR) that is closely related to ovarian endometrioma. The difference in findings are due to the different severity of the disease, the presence or absence of endometrioma, and different therapies received. Other than that, there is a chance of the non-endometriosis samples have the disease but undiagnosed. This research also does not study about the IVF processes.

5. Maternal Age

The Chi-Square test showed a p value of 0.037 meaning there is a relationship between maternal age and IVF outcome. And for the Binary Logistic Regression test, the p value is 0.044 for age group 36-40 years old. The OR results were found as follows, women in the age group of 36-40 years old have a 2.397 times higher risk of IVF failure than women aged 25-35 years old. For women aged >40 years old, the risk increased 4.827 times than 25-35 year-olds. Therefore, the highest risk of IVF failure for all age group is >40 years old. The statistical analyses showed aligned results and we can infer that maternal age have a relationship with and affects IVF outcome. The same is found in other studies, maternal age have a significant effect on IVF outcome. This is can be seen through the total cycle that reached embryo transfer stage with a p value <0.001 and the total oocyte retrieved decreases along with the increase of age group with a p value <0.001, while the highest amount is found in age group <30 years old. The increase of age is directly proportional with a decrease of fertilization rate and has a significant effect on clinical pregnancy rate, live birth rate, and multiple pregnancies. The study concluded out of all age groups, <30 year-olds have the best rate for IVF outcome. Other studies also reported biochemical pregnancy rate, implantation rate, clinical pregnancy, and live birth are all higher in age group <35 years old, while in ≥35 year-olds there is an increase wof spontaneous abortion rate and biochemical pregnancy failure. This phenomenon is explained in a study, maternal age affects the fertilization rate and embryo development to blastocyst, causing an increase of aneuploidy rate from 30% in <35 year-olds to 90% in >44 year-olds. Along with the progressive decrease of ovarian reserve, maternal age is related to a decrease in oocyte quality caused by damaged physiological pathways including epigenetic regulation and metabolism.

Conclusion

This research concluded that maternal age is the most significant factor that affects the outcome of IVF. Regarding other variables, sperm abnormality, maternal BMI, and endometriosis do not affect the outcome of IVF significantly. And the data for

maternal smoking habits are insufficient. However, the failure of IVF itself consists of numerous other factors that include both sides of the couple, hence one-sided blame should be avoided. Therefore, the failure outcome of IVF should be evaluated holistically and psychological support for both sides should be facilitated.

The following are things that should be taken into consideration regarding this research's conclusion. There are key factors that are not studied in this research, which include the implementation of each step of the procedure, along with the technique and technology used. Other factors that might contribute, including polycystic ovarian syndrome (PCOS), diminished ovarian reserve (DOR), and estradiol levels are also not studied. And last, the limited sample size.

This research has brought about some suggestions. We highly recommend shifting to digital medical records to minimize insufficient data and misplacing. Data about maternal smoking habits should be added progressively in medical records so that its effect can be further analyzed. For the general public, it is highly discouraged to postpone pregnancy plans considering the effect of maternal age. For the researcher hereafter, research with a bigger sample size and a more detailed inclusion and exclusion criteria must be conducted. We also hope that key factors that are not studied in this research and the effect of maternal smoking habits can be reviewed for further study.

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