

COMPARATIVE ANALYSIS OF WOMEN AGED OVER 35 AFTER *IN VITRO* FERTILISATION AND NATURAL FERTILISATION: A CASE CONTROL STUDY

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Postponing motherhood is a worldwide trend. As a woman ages, the ability to get pregnant naturally decreases. The postponement of motherhood is related to the increased availability of assisted reproductive technology, which is associated with a higher incidence of maternal health problems.

Aim of the study: To compare the health problems encountered during pregnancy, childbirth and early postpartum, and to examine the health status of the newborn, in women over 35 years of age who received *in vitro* fertilisation (IVF) or conceived naturally.

Material and methods: A retrospective comparative case-control study was carried out based on the analysis of medical records from women who gave birth after 35 years of age. The study was conducted in two hospitals of the third level of reference in Warsaw, Poland. A group of women who gave birth after IVF (n=240) was compared with a control group who gave birth following natural fertilisation (n=240).

Results: Women after IVF were statistically more likely to be obese (5% vs 0.2%, p=0.001), to have received infertility treatment (18% vs 1%, p=0.000) before pregnancy, and to experience cholestasis during pregnancy (4% vs. 1%, p=0.019). There was a higher incidence of multiple pregnancies [twins (10% vs 1%, p=0.0001) and triplets (0.5%, p=0.0001)], and deliveries by caesarean section (61% vs 51%, p=0.027) in women from the IVF group. The groups did not differ with respect to preterm delivery, duration of pregnancy, or 1st, 2nd and 3rd periods of labour. Mothers in the IVF group had a statistically longer perinatal hospital stay (7±8 vs 5±4 days, p=0.001).

Conclusions: Women over 35 years of age after IVF have a higher rate of caesarean sections and multiple pregnancies. Obesity before pregnancy and cholestasis during pregnancy are also more common in this group. There is no difference between the health status of newborns from mothers after *in vitro* or natural fertilisation.

KEYWORDS: maternal age, *in vitro* fertilisation, gravidity

BACKGROUND

Postponing motherhood is a worldwide trend. Today, women planning to procreate take into consideration their plans for education, a professional career and a regular partner, especially in the case of a first pregnancy [1, 2]. In Poland, the average age of women giving birth has increased by about 2 years over the last 10-year period. In 2009, the average age of giving birth to the first child was 25.82 years and the average age of all women giving birth was 27.96 years. In 2019, these values increased to 27.82 years and 29.91 years, respectively [3].

As a woman ages, the ability to get pregnant naturally decreases. This is due, in part, to factors like a reduced ovarian reserve, and past health and gynaecological problems that negatively affect fertility [4]. Studies have observed positive associations between infertility, cardiovascular issues, insulin resistance, increased BMI, and metabolic syndrome, suggesting that this condition should not be perceived as an isolated disease affecting only the reproductive system [5, 6]. Legislation regulating the treatment of infertility indicates that care should begin with a medical consultation and diagnosis of the causes of infertility, followed by the use of assisted procreation procedures after any pharmacological or surgical treatments [7].

Postponing motherhood is also related to an increase in the availability of assisted reproductive technology (ART). The most commonly used ART methods are *in vitro* fertilisation (IVF) and intrauterine insemination, with IVF being the most effective method in cases of advanced maternal age [8, 9]. The development of pre-implantation diagnostic methods has also allowed for the detection of genetic defects even before embryo implantation. These latter procedures have increased the chances of older women bearing healthy children [10,11].

Research shows that the use of ART increases the incidence of maternal health problems such as hypertension and gestational diabetes relative to women conceiving naturally, and the occurrence of preterm birth and lower birth weight in the newborn is elevated [12,13]. Multiple pregnancies are more common following the application of ART than with natural insemination, which may be one of the reasons for increased health care costs [8,14].

Most previous studies examining the health of mothers have compared mothers over the age of 35 to younger women. Here, we compare a group of mothers aged 35 years and older who have given birth following IVF or natural fertilisation.

AIM OF THE STUDY

The aim of this study was to compare women giving birth over the age of 35 that had either conceived

naturally or received IVF treatment. Potential differences in health problems during pregnancy, childbirth, and early postpartum, and the health status of the newborn, were examined. The data obtained may be helpful in planning holistic obstetric care during pregnancy, delivery and postpartum for these groups of mothers.

MATERIAL AND METHODS

Study design

A retrospective comparative case-control study was carried out based on the analysis of medical records from women who gave birth after 35 years of age.

Settings

The study was conducted on records obtained from two hospitals of the third level of reference in Warsaw, Poland between February 1, 2017 and January 31, 2019.

Participants

The participants were divided into two groups based upon the selection criteria outlined below. The study group (n=240) was comprised of women over the age of 35 years who gave birth following IVF treatment. This group consisted of both first-born women (n=178) and multiparous women (n=62). The control group (n=240) consisted of women aged 35 years and older who gave birth after natural fertilisation, and also included primiparous (n=178) and multiparous women (n=62).

The inclusion criteria for the study group were an age over 35 years, delivery after completing at least 22 weeks of pregnancy, and IVF treatment. The exclusion criteria for this group were an age below 35 years, natural insemination, and delivery before 22 weeks of gestation.

The inclusion criteria for the control group were an age of 35 years or older, delivery after at least 22 weeks of pregnancy, and natural insemination. These criteria resulted in a large sample (n=3829). In an effort to match the number of mothers in the study group, a smaller number of participants were randomly selected from this larger sample. From the overall group of primiparas (n=1007), 178 cases were randomly selected for study, and from the group of multiparas (n=2822), 62 cases were randomly selected. A schematic showing the stages of sample selection for the study is shown in Figure 1. The ages of mothers included in the study and control groups are shown in Table 1.

Table 1. Age and count of women in the groups

Age	Study group – IVF* (n=240)		Control group – NAT* (n=240)	
	primiparas (n=178)	multiparas (n=62)	primiparas (n=178)	multiparas (n=62)
35	41 (23.03%)	13 (20.97%)	41 (23.03%)	13 (20.63%)
36	32 (17.97%)	11 (17.74%)	32 (17.97%)	12 (19.04%)
37	20 (11.23%)	10 (16.13%)	20 (11.23%)	9 (14.52%)
38	21 (11.80%)	7 (11.29%)	21 (11.80%)	7 (11.29%)
39	20 (11.24%)	6 (9.67%)	20 (11.24%)	6 (9.67%)
40	18 (10.11%)	6 (9.67%)	18 (10.11%)	6 (9.67%)
41	8 (4.49%)	3 (4.84%)	4 (2.25%)	1 (1.61%)
42	5 (2.80%)	3 (4.84%)	5 (2.80%)	2 (3.23%)
43	4 (2.25%)	1 (1.61%)	6 (3.37%)	1 (1.61%)
44	1 (0.56%)	0	6 (3.37%)	1 (1.61%)
45	4 (2.25%)	0	3 (1.69%)	1 (1.61%)
46	1 (0.56%)	1 (1.61%)	1 (0.56%)	1 (1.61%)
47	1 (0.56%)	0	1 (0.56%)	2 (3.23%)
48	1 (0.56%)	0	0	0
49	1 (0.56%)	0	0	0
56	0	1 (1.61%)	0	0

* IVF – *in vitro* fertilisation, NAT – natural fertilisation

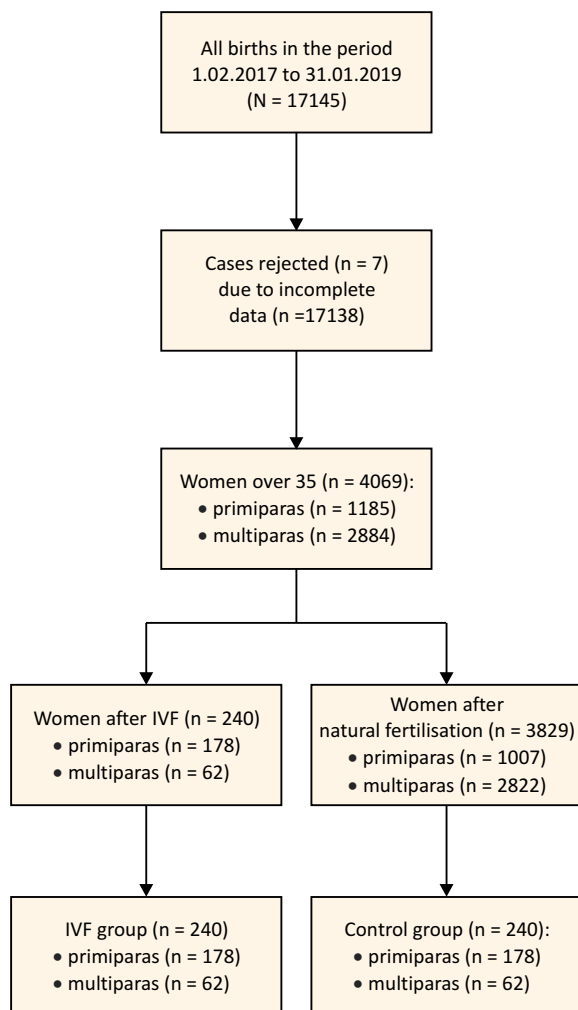


Figure 1. Selection of sample

Dependant variables

The study included the following data: (1) Women's health status before pregnancy as indexed by the number of previous miscarriages, presence of hypertension and obesity, presence of uterine myomas, and any treatments for infertility. (2) Health problems that occurred during pregnancy including cholestasis, diabetes, hypertension and hypothyroidism. (3) The week of gestation, the number of foetuses, the route and method of delivery, the duration of the 1st, 2nd and 3rd periods of delivery, and complications occurring during delivery such as premature discharge of amniotic fluid and incomplete afterbirth. (4) Problems occurring in early puerperium such as anaemia and duration of maternal hospitalisation. (5) The health of the newborn at birth as measured by the weight, length, and Apgar score in the first minute after birth.

Preterm birth was defined as births completed between 22 and 37 weeks of gestation. Infertility treatment was defined as interventions to recover fertility through conservative and surgical methods. Obesity was defined as a BMI above 25. Gestational diabetes mellitus (GDMG) and pregnancy-induced hypertension (PIH) were defined based on the 2018 Polish Standards of Perinatal Care [15]. Premature rupture of membranes (PROM) was defined as rupture of the membranes before labour begins. Perinatal hospitalisation time was defined as the continuous number of days a woman was hospitalized from admission to hospital to discharge after delivery.

This study was approved by the Bioethics Committee of the Warsaw Medical University (AKBE/214/2017).

Statistical analyses

Analyses were performed using Statistica 13.1 software. Continuous variables were compared using Student's *t*-test or the Mann-Whitney *U* test, and proportional data were compared using the Chi square test. $p < 0.05$ was used as the level of significance. Results are presented as mean±standard deviation or percentages.

RESULTS

During the study period, 17145 deliveries took place in both hospitals. Of these, 23.7% occurred in women over 35 years of age ($n=4071$).

The groups of women after IVF and natural insemination were similar with respect to age (37.91 ± 2.91 vs. 37.94 ± 2.86 years, $p=0.961$). The oldest patient in the IVF group was 56 years old and after natural insemination 47 years old. The largest group in terms of age was women aged 35 years with 54 women each in the control and study groups. Primiparas ($n=178$) constituted 74% of the study group.

There was no increased incidence of miscarriage in the group of women after IVF (30% vs. 36%, $p=0.242$). However, this group was statistically more likely to be obese before pregnancy (5% vs. 0.2%, $p=0.001$; Table 2).

Table 2. Group characteristics

Variable	IVF group (n=240)	Control group (n=240)	p-value
Age of mother (years)	37.93 (± 2.99)	37.94 (± 2.86)	0.961
Miscarriages:			
1	43 (18%)	61 (25%)	0.242
2	18 (7%)	14 (6%)	
>2	12 (5%)	11 (5%)	
Myomas	15 (6%)	6 (2%)	0.044*
Infertility treatment	44 (18%)	3 (1%)	0.000*
Obesity	11 (5%)	1 (0.2%)	0.001*
Pre-pregnancy hypertension	11 (5%)	5 (2%)	0.127

* $p < 0.05$.

The health status of pregnant women did not differ between groups in the prevalence of GDMG (17% vs. 12%, $p=0.094$), PIH (6% vs. 7%, $p=0.706$), and hypothyroidism (32% vs. 24%, $p=0.057$). However, women after IVF were statistically more likely to be diagnosed with cholestasis during pregnancy (4% vs. 1%, $p=0.019$; Table 3).

Table 3. Pregnancy-related health problems.

Variable	IVF group (n=240)	Control group (n=240)	p-value
Cholestasis	10 (4%)	2 (1%)	0.019*
GDMG	42 (17%)	29 (12%)	0.094
PIH	20 (8%)	17 (7%)	0.608
Hypothyroidism	76 (32%)	58 (24%)	0.067

* $p < 0.05$.

In the study group, there was a higher incidence of multiple pregnancies [twins (10% vs. 1%, $p=0.0001$) and triplets (0.5%, $p=0.0001$)] and deliveries by caesarean section (61% vs. 51%, $p=0.027$). The groups did not differ with respect to preterm delivery (13% vs. 9%, $p=0.189$), duration of pregnancy (38 ± 2.45 vs. 38.7 ± 2.54 weeks, $p=0.270$), or duration of 1st period (298 ± 164 vs. 339 ± 202 min, $p=0.108$), 2nd period (34 ± 32 vs. 47 ± 80 min, $p=0.218$), and 3rd periods of labour (11 ± 12 vs. 10 ± 9 min, $p=0.890$). There also was no statistical significance between groups for operative delivery (5% vs. 7%, $p=0.241$), incomplete afterbirth (2% vs. 4%, $p=0.189$), and occurrence of secondary anaemia after delivery (6% vs. 7%, $p=0.852$). Mothers in the study group had a statistically longer perinatal hospital stay (7 ± 8 vs. 5 ± 4 days, $p=0.001$; Table 4).

Table 4. Delivery and early puerprnium-related problems

Variable	IVF group (n=240)	Control group (n=240)	p-value
Number of foetuses:			
1	215 (90%)	237 (99%)	<0.001*
2	24 (10%)	3 (1%)	
3	1 (0.5%)	0	
Week of pregnancy	38 (± 2.45)	38 (± 2.54)	0.270
Premature birth	31 (13%)	22 (9%)	0.189
Method of delivery:			
vaginal childbirth	94 (39%)	118 (49%)	0.027*
caesarean section	146 (61%)	122 (51%)	
Instrumental delivery (forceps, vacuum)	12 (5%)	7 (3%)	0.241
Duration of stages of labour (min)**:			
first stage	298 (± 164)	339 (± 202)	0.108
second stage	34 (± 32)	47 (± 80)	0.218
third stage	11 (± 12)	10 (± 9)	0.890
PROM	26 (11%)	39 (16%)	0.082
Placental abruption	5 (2%)	10 (4%)	0.189
Secondary anaemia	15 (6%)	16 (7%)	0.852
Hospitalisation time	7 (± 8)	5 (± 4)	0.001*

* $p < 0.05$.

** Vaginal childbirths alone.

In the group of women after IVF (n=240), 266 children were born, 24 pregnancies were twins, and one was a triplet. In the group of women after natural insemination (n=240), there were 243 children born, including 3 cases of twin pregnancies. Neonatal health did not differ significantly between groups for weight (3140±756 vs 3240±5673g, p=0.171), length (53±6 vs 53±5cm, p=0.705), and Apgar score after 1 minute of life (9.66±1 vs 9.62±1.41, p=0.353; Table 5).

Table 5. Newborn condition

Variable	IVF group (n=266)	Control group (n=243)	p-value
Weight (g)	3140 (±757)	3240 (±673)	0.171
Length (cm)	53 (±6)	53 (±5)	0.705
Apgar score after 1 min	9.66 (±1)	9.62 (±1.41)	0.353

Discussion

Our study has shown that women over 35 years of age after IVF are more likely to have uterine myomas and obesity, to previously have been treated for infertility, and to experience cholestasis during pregnancy. This method of insemination is more likely to result in the occurrence of multiple pregnancies, and thus the associated higher number of caesarean sections and longer perinatal hospitalisation time observed in this group.

Most previous studies in this area have focused on comparing the health status of mothers over 35 to younger women, finding a link between maternal age and the occurrence of health problems during pregnancy, childbirth and postpartum [1, 17, 18]. The frequency of ART interventions is related not only to women's age but also to childbearing. Studies show that among women who have received ART, the majority are primiparous [17, 19, 20]. A similar trend was found in our study group, where primiparas accounted for as much as 74% (n=178) of participants.

Infertility treatment is typically defined as the exclusive use of ART methods [21]. In Poland, the definition of infertility treatment, according to the Act on Infertility Treatment, also includes conservative and surgical methods leading to the recovery of fertility, such as treatment of co-morbidities or removal of the causes of infertility with available surgical methods (laparoscopy, hysteroscopy) [7]. In our study, women after IVF were significantly more likely to have received infertility treatment that allowed them to become pregnant (18% vs. 1%, p=0.000).

Obesity, an increasingly common problem among women of reproductive age, is one of the factors affecting fertility. Hormonal problems that occur with obesity can negatively affect ovulation, fertilisation and embryo implantation [22]. However, a meta-

analysis of studies on obesity among pregnant women has indicated that there is no association of obesity with health problems occurring during pregnancy and the health of the newborn [24]. In our study, obesity was statistically more frequent among women after IVF than in the control group (11% vs. 0.2%, p=0.001). However, we also found no statistically significant correlation between obesity and women's health problems.

There were 765647 births between 2018 and 2019 in Poland, and births to women over 35 accounted for 18.9% (n=145114) of the total. During this period, 9.4% of women over 35 years of age gave birth prematurely (n=13696). Twin pregnancies occurred in 3%, and triplet pregnancies in 0.8%, of the population of women over 35 years of age [3]. During the study period, a total of 17145 births took place in both hospitals examined and births over 35 years of age accounted for 23.7% (n=4071) of the total. A report by The European IVF-monitoring Consortium for the European Society of Human Reproduction and Embryology identifies the number of embryos transferred as a reason for more multifetal pregnancies [9]. In our study, twin and triplet pregnancies occurred significantly more often (10%, n=24 and 0.5%, n=1, respectively) in women after IVF compared to the control group, where twin pregnancies occurred in 1% of women (n=3).

In similar research examining the differences between groups after *in vitro* and natural insemination, Zhu et al. reported a higher incidence of pregnancy-induced diabetes and hypertension, cholestasis, placenta previa, and multiloculation in women receiving IVF [24]. However, in our study, only a higher prevalence of cholestasis was observed in the IVF group (10% vs. 1%, p=0.019).

Preterm birth has been reported as a more common complication among women after IVF, and also as a consequence of multiple pregnancies in some studies [25–28]. In our study, despite the higher number of multiple pregnancies in the IVF group, there were no statistically significant differences in the incidence of preterm births or neonatal health between the study and control groups.

During the study period, the percentage of caesarean sections among all women over 35 years of age was 40% in both hospitals. Our results show that the caesarean section rate is increased in women over 35 years of age receiving IVF, as the incidence in the control group was 51%, and in the IVF group 61%. Similar results have been shown by studies around the world. Studies in Finland and the United States show similar relationships between the use of ART techniques and increased caesarean section rates [29, 30].

In the study by Heo et al., no differences were found in the occurrence of maternal health problems and birth weight of the newborn following IVF

or natural insemination [31]. Similarly, in our study, newborns of mothers from both groups did not differ statistically between each other in terms of weight and Apgar scores at the first minute of life (3140 ± 757 vs. 3240 ± 673 g, $p=0.171$).

Limitations of the study

A limitation of our study is the lack of data on the prevalence of some diseases such as pre-pregnancy diabetes, and sociometric data including the degree of education, diet or maternal smoking were not examined. In addition, the variables of placenta previa, asthma, diabetes diagnosed before pregnancy, and

pre-eclampsia were omitted from the study due to the low number of cases.

CONCLUSIONS

Women over 35 years of age after IVF have a higher rate of caesarean sections and multiple pregnancies. Obesity before pregnancy and cholestasis during pregnancy are more common in this group. The health status of newborns of mothers after IVF and mothers after natural fertilisation does not differ. Children of women over 35 years of age, regardless of the method of conception, are born in good condition.

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