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Assessment of the birth status of children born by elective caesarean section before and after 39 weeks of gestation following in vitro fertilization

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ABSTRACT

The collected material presents 512 mothers with children whose pregnancies were ended by caesarean section at the Department of Obstetrics, Women's Diseases and Oncological Gynecology Central Clinical Hospital of the Ministry of Internal Affairs in Warsaw in the years 2004–2016. The study group consisted of 362 mothers in pregnancies following *in vitro* fertilization and 150 mothers in spontaneous pregnancy, without the use of assisted reproductive technology. For the purposes of the project, only single pregnancies ending within weeks 37 to 41 of pregnancy were selected.

Planned delivery by elective cesarean section (ECS) currently takes place after the 39th week of pregnancy, in line with current common recommendations. This is related to studies finding an overall better birth condition of newborns in the general population, and especially regard-

ing the maturation of the lungs. Currently, there are no specific recommendations regarding cesarean section and the timing of delivery in pregnancies resulting from *in vitro* fertilization.
The aim of this study was to assess the optimal time of an elective cesarean section at full term in an IVF pregnancy. Consistent with findings in the general population and prevailing recommendations, the expected result would be the better condition of the baby born by ECS following the 39th week of gestation.
However, our statistical analysis of the collected material shows that the group delivered by ECS prior to the end of 39 weeks of pregnancy may have fewer respiratory system interventions and higher Apgar scores. Nevertheless, results lack statistical significance. In conclusion these findings may indicate a need for a bigger database.

Key words: IVF; neonatal health; cesarean section

INTRODUCION

In vitro fertilization techniques are often the last option for fulfilling long-awaited maternal plans. Models of family planning in contemporary society are changing and the average age of a mother giving birth to her first child is increasing; and with the older age of maternity the probability of spontaneous pregnancy is decreasing. If we also take into consideration that a certain percentage of the population will have undiagnosed infertility, assisted reproductive technology will be a last resort for many women wishing to fulfill their maternal needs. In Poland, according to Central Statistical Office data, the average age of a primigravida in 2017 was 27.8 years, compared with the average age of women in the general population giving birth of 31.1 years [1].

Studies show that assisted reproductive technology (ART) pregnancies differ from those in the general population of natural pregnancies, and that *in vitro* fertilisation influences the course of pregnancy [2–4]. As maternal age increases, the likelihood of successful embryo transfer with successful pregnancy and delivery decreases [5]. Increased incidence of pregnancy-induced hypertension has been observed in single pregnancies resulting from in vitro fertilisation in women aged 30 to 34 years, and in those aged ≥ 40 years [2–4]. Other studies [6] found that older pregnant women have an increased risk of gestational diabetes, are significantly more likely to deliver by cesarean section (78.5% compared to a younger control group of 28.9%) [7], and have an increased risk of placental separation. Given that older maternal age increases the probability of complications during the pregnancy as well as delivery [7], it is likely that women with ART pregnancies who are usually of a more advanced maternal age, will encounter a similar risk of complications. Studies of Waldenström U and al and Lean SK and al, of pregnant women in the general population women older than 35 years show an increased likelihood of intrauterine fetal death (increasing with maternal age and weeks of gestation), preterm delivery, low or very low neonatal birth weight, neonatal intensive care unit admission, and pregnancy complications such as gestational diabetes and pregnancy-induced hypertension [8, 9]. However, more cases of hypertension were detected in the more advanced age group and in pregnancies after IVF/ICSI procedures, which again shows that ART pregnancies may differ from the normal population.

Patients with a high-risk pregnancy are offered delivery by elective cesarean section. After the 39th week of gestation is said to be the optimal time for a cesarean section that balances the benefits and risks of the procedure for both mother and the child. Recommendations about the timing of Caesarean sections [10, 11] indicate an increased risk of respiratory morbidity in children born by this method prior to spontaneous labour. For pregnancies resulting from *in vitro* fertilisation, general recommendations are made. Currently, there are no specific recommendations regarding cesarean sections and the optimal timing of delivery for pregnancies resulting from artificial reproduction techniques.

The purpose of our study was to compare the state of neonates, grouped according to their gestation age at the date of birth. Cesarean delivery, even in full term births, is associated with a higher incidence of respiratory distress [12]. Delayed or impaired clearance of fluid from the neonate's lungs after birth leads to clinical manifestations in post-term life of minor or more severe respiratory distress syndromes: transient tachypnea of the newborn with a respiratory rate > 60/min, abnormalities of respiratory rhythm, apneic seizures, and respiratory distress syndrome (RDS) [13]. Neonates may also present with hypoxia, hypo or normocapnia (less commonly with hypercapnia), and metabolic or respiratory acidosis. Interventions in the neonatal respiratory system may have consequences in later life. Singleton pregnancies after IVF have a higher incidence of reduced Apgar scores and respiratory problems during childhood [14]. Respiratory interventions in the early life of the newborn may affect the incidence of disease in later life, such as asthma [15].

The aim of this study was to assess the optimal time of an elective cesarean section at full term in an IVF pregnancy. The expected result would be the better condition of the baby born by ECS following the 39th week of gestation as in general population, although differences occurring in IVF pregnancies may affect that timing.

MATERIAL AND METHODS

Study design and patients

Our study assesses data from 512 mothers whose pregnancy ended by cesarean section, performed in the Department of Obstetrics, Women's Diseases and Oncological Gynecology Central Clinical Hospital of the Ministry of Internal Affairs in Warsaw, during the years 2004 to 2016. The study group consisted of 362 mothers in pregnancies following *in vitro* fertilization (IVF) and 150 mothers in spontaneous pregnancy, without the use of assisted reproductive technology (ART). We examined the medical histories of the mothers and children included in the study. The acquired parameters (time of delivery of pregnancy, maternal age, details of caesarean section, whether glucocorticoids were used before cesarean section, Apgar score of the newborn, and whether respiratory medical interventions took place) were analysed to assess the condition of each neonate. The respiratory complications of the newborn were classified into two groups — minor respiratory interventions (complications such as transient tachypnoea of the newborn or infant respiratory distress syndrome without the need of serious medical interventions) and major respiratory interventions (requiring more extensive interventions such as need of oxygen therapy for over two days, mechanical ventilation, or use of continuous positive airway pressure ventilation). Multiple pregnancies, pregnancies with birth of either < 37 weeks or > 41 weeks of gestation, neonates with sepsis, pneumonia, meconium aspiration syndrome, and those which underwent a course of steroid therapy prior to their cesarean section were excluded from the study as these cases could have affected respiratory morbidity regardless of the method or time of delivery. For the purposes of our statistical and correlation analyses, having divided the pregnant women in our study group into four (elective CS delivery after IVF prior to 39 weeks, elective CS delivery after IVF after 39 weeks, elective CS delivery without the use of IVF after 39 weeks, and emergency CS delivery after IVF) we compared their data analysis results for each of the variables listed above, with time of delivery (weeks of gestation).

The data of singleton pregnant mothers and their neonates delivered by caesarean section following *in vitro* fertilization were extracted from the hospital's birth register. Subsequently, maternal medical data, details of caesarean section, neonatal assessment data were extracted from the full medical histories for each mother and newborn.

The pregnant women were divided into 4 groups:

1.Those delivered by elective cesarean section after the end of 39 weeks of gestation after IVF.

2. those delivered before the end of 39 weeks of gestation after IVF,

3. those delivered after the end of 39 weeks of gestation without the use of IVF, and

4. those delivered by emergency cesarean section after IVF (due to urgent indications, e.g., the onset of contractions, or premature rupture of amniotic membranes) .

Assignment of each woman to a particular group was made retrospectively based on data from the patient's medical records.

Study inclusion/exclusion criteria

For inclusion, we selected women with singleton pregnancies following in vitro fertilization, whose pregnancies ended within the 37th to 41st weeks of gestation, and women with singleton pregnancies without the use of in vitro fertilization, whose pregnancies ended after 39th weeks of gestation. For the group of mothers with children born after elective cesarean section without the use of IVF was chosen women with comorbidities that contradicted the vaginal delivery, such as ophthalmic, neurological (e.g. epilepsy), orthopedic (e.g. after spine injuries), obstetric (e.g. breech birth, after two post-cesarean section condition) or psychiatric (e.g. tokophobia) reasons.

Those excluded were women with twin pregnancies, pregnancies of either < 37 weeks or > 41 weeks of gestation, and neonates with meconium aspiration syndrome, sepsis, or pneumonia, those which underwent a course of steroid therapy prior to their cesarean section, because those cases may have affected respiratory morbidity regardless of the method or timing of their delivery.

Statistical analysis

Statistical analysis was performed using Statistica 13.1 software (StatSoft Poland). Mean values and standard deviations were used to describe the three study groups of pregnant women, in case of skewed distributions the median was calculated as a measure of central tendency, the scatter was presented using the quartile range, and in case of qualitative variables the data were presented as a percentage.

After assessing the normality of the distributions of explanatory variables using the Shapiro-Wilk test, a comparative analysis of individual groups was performed.

Because the assumptions of a near-normal distribution were not met, Kruskall-Wallis analysis of variance with Dunn's post hoc test was used to compare the groups.

In the case of qualitative variables, Pearson's Chi2 test was used to compare the frequency of the studied characteristics in the groups. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Whole group study

The study included 512 patients comprised of four subgroups: In Group 1, there were 162 women (31.64% of the total) delivered by elective caesarean section after the 39th week of gestation after IVF; in Group 2, 82 women (16.01%) delivered by elective caesarean section before the 39th week of gestation after IVF; in Group 3, 150 women (29.3%) delivered by elective cesarean section after 39th week of gestation in pregnancies without the use of IVF, and in Group 4, 118 women (23.05%) delivered by emergency caesarean section (for obstetric reasons including failure to progress in labour, or premature rupture of amniotic membranes).

The distribution of the women's demographic variables (mother's age, weeks of gestation) between the groups is shown below (Tab. 1 and Tab. 2).

Table 1. Distribution of maternal ages between groups

Variable: mother's age in groups			
Study group	**Mean**	**Median**	Inter Quartile Range
Group 1	35.43	35.50	5.00
Group 2	34.73	34.00	6.00
Group 3	30.13	29.00	5.00
Group 4	34.70	34.00	4.00

Table 2. Distribution of gestation age between groups

Variable: week of gestation			
Study Groups	**Mean**	**Median**	Inter Quartile Range
Group 1	39.08	39.00	0.00
Group 2	37.91	38.00	0.00
Group 3	39.39	39.00	1.00
Group 4	38.24	38.00	1.00

Apgar scores and respiratory interventions were then assessed against the study groups for qualitative tests. Comparisons of groups for neonatal blood pH at birth were not examined due to missing results in 86% of cases.

Contingency tables are shown below (Tab. 3 and Tab. 4). For neonatal Apgar scores, a division was established: class 1 — general good condition (8–10 Apgar points), class 0 — medium condition (4–7 points). Neonates in severe general condition (1–3 points in Apgar score) were not recorded. A Chi2 test with a calculated "p" factor is shown under each contingency table.

Table 3. Frequency of observed neonatal Apgar parameters between groups

	Summary bivariate table: observed frequencies in Apgar score							
Study Groups	**Apgar 1' 8–10 points**	**Apgar 1' 4–7 points**	**Apgar 3' 8–10 points**	**Apgar 3' 4–7 points**	**Apgar 5' 8–10 points**	**Apgar 5' 4–7 points**	**Apgar 10' 8–10 points**	**Apgar 10' 4–7 points**
1	158	4	161	1	162	0	162	0
% of group	97.53%	2.47%	99.38%	0.62%	100%	0%	100%	0%
2	82	0	81	1	82	0	82	0
% of group	100%	0%	98.78%	1.22%	100%	0%	100%	0%
3	148	2	150	0	150	0	150	0
% of group	98.67%	1.33%	100%	0%	100%	0%	100%	0%
4	112	6	116	2	116	2	117	1
% of group	94.92%	5.08%	98.31%	1.69%	98.31%	1.69%	99.15%	0.85%

A. Apgar score at 1 minute of life of the newborn

Table 4. Statistical significance of the parameter Apgar scores of newborns at 1' of life in groups according to Pearson/NW

Statistics	**Statistics: Apgar 1' [0–4–7, 1–8–10] (2) × study groups**		
	Chi2	df	p
Chi2 Pearson	6.521568	Df = 3	p = 0.0892
Chi2 NW	7.607854	df =3	p = 0.05485

The result is on the verge of statistical significance of $p < 0.05$ (Chi2 NW p = 0.5485).

B. Apgar score in the remaining minutes of the neonatal assessment (at 3, 5 and 10 minutes of the neonatal Apgar score) in the analysis showed no statistically significant difference ($p > 0.05$). However, the trend towards better scores in neonatal assessment persisted in group 2.

C. Respiratory complications of the newborn.

Table 5. Frequency of observed respiratory complications in the newborn between groups

Type of respiratory intervention	**Study Group 1**	**Study Group 2**	**Study Group 3**	**Study Group 4**
0 — no respiratory interventions	149	78	145	107
% of group	93.12%	95.12%	96.67%	90.68%
1 — minor respiratory interventions	9	2	5	8
% of group	5.62%	2.44%	3.33%	6.78%
2 — major respiratory interventions	2	2	0	3
% of group	1.25%	2.44%	0%	2.454%
General number	160	82	150	118

Table 6. Statistical significance of the parameter of minor respiratory complications in groups according to Pearson/NW

Statistics	Statistical significance of the parameter of minor respiratory complications in groups according to Pearson/NW		
	Chi2	Df	p
Chi2 Pearson	3,002796	Df = 3	P = 0.39119
Chi2 NW	3,117150	Df = 3	P = 0.37391

Table 7. Statistical significance of the parameter of major respiratory complications in groups according to Pearson/NW

Statistics	Statistical significance of the parameter of major respiratory complications in groups according to Pearson/NW		
	Chi2	**Df**	**p**
Chi2 Pearson	3.987061	Df = 3	P = 0.26286
Chi2 NW	5.678871	Df = 3	P = 0.12832

In Group 1 it was not possible to obtain data about respiratory complications of the newborn in two cases.

The highest number of complications was observed in Group 3, after emergency caesarean sections, in both minor and severe respiratory interventions. In Group 2, the percentage of respiratory interventions was the lowest, that is altogether 5.08% from the group (Tab. 5). However, the analysis showed no statistically significant difference ($p > 0.05$) (Tab. 6).

To identify possible reasons for the higher numbers of worse neonatal outcome cases of group 1 compared to the other groups, we observed that the noticeable higher mean of the maternal ages in Group 1 compared to the other groups, could be a potential cause. Therefore, the study groups were re-evaluated, this time focusing on women ≥ 35 years of age.

Study of the group with mothers ≥ 35 years of age

In total there were 216 women ≥ 35 years — which comprised 42.2% of the total group of 512 women. Correspondingly, that figure sub-divided into 99 women (45.83%) in Group 1, 37 women (17.13%) in Group 2, 28 women (12.96%) in Group 3, and 52 women (24.07%) in Group 4 (Tab. 7).

Table 8. Age distribution of mothers who are ≥ 35 years

Variable: mother's age in groups ≥ 35 years of age			
Study Group	**Mean**	**Median**	**Inter Quartile Range**
1	37.88889	37.0	3.00
2	38.45946	38.0	4.00
3	37.07	37.0	3.50
4	38.42	37.5	4.00

After considering mothers aged ≥ 35 years, Group 2 is older than Group 1. This result is different from the study of the general population, where Group 1 was the oldest.

Table 9. Frequency of observed neonatal Apgar parameters in subjects with maternal age ≥ 35 years, compared by group

Study Groups	Summary bivariate table: observed frequencies (IVF adherence) in groups ≥ 35 years of age							
	Apgar 1' 8–10 points	**Apgar 1' 4–7 points**	**Apgar 3' 8–10 points**	**Apgar 3' 4–7 points**	**Apgar 5' 8–10 points**	**Apgar 5' 4–7 points**	**Apgar 10' 8–10 points**	**Apgar 10' 4–7 points**
1	95	4	98	1	99	0	99	0
% of group 1	95.96%	4.04%	98.99%	1.01%	100.00%	0.00%	100.00%	0.00%
2	37	0	37	0	37	0	37	0
% of group 2	100.00%	0.00%	100.00%	0.00%	100.00%	0.00%	100.00%	0.00%
3	28	0	28	0	28	0	28	0
% of group 3	100.00%	0.00%	100.00%	0.00%	100.00%	0.00%	100.00%	0.00%
4	50	2	51	1	51	1	51	1
% of group 4	96.15%	3.85%	98.08%	1.92%	98.08%	1.92%	98.08%	1.92%

A. Apgar score at 1 minute of life of the newborn aged ≥ 35 years

Table 10. The statistical significance of the parameter Apgar score of newborns at 1' of life in groups according to Pearson/NW after adjusting to include only mothers ≥ 35 years of age

Statistics	Statistics: Apgar 1' [0–4–7, 1–8–10] (2) × study groups		
	Chi2	**Df**	**p**
Chi2 Pearson	2.661339	Df = 3	p = 0.44684

Statistics	Statistics: Apgar 1' [0–4–7, 1–8–10] (2) × study groups		
	Chi2	**Df**	**p**
Chi2 NW	4.372772	Df = 3	p = 0.22392

Compared with the whole study group of 512 mothers and newborns (excluding mothers aged ≥ 35 years), there result is without statistically significant differences in Apgar scores at 1 minute of neonatal life. Compared with the whole group regardless of mothers' ages, the lowest number of Apgar scores 4–7 points after pregnancy involving IVF was found in Group 2 and Group 3 (Tab. 8).

B. Apgar scores at 3, 5 and 10 minutes of neonatal life in groups with mothers aged ≥ 35 years

There was no statistically significant difference in Apgar scores at 3, 5, and 10 minutes of neonatal life. The trend of worse scores tends to persist in Group 4.

C. Respiratory complications in groups ≥ 35 years

Table 11. Frequency of observed respiratory complications in the newborn between groups with mothers who aged ≥ 35 years

Type of respiratory intervention	Study Group 1	Study Group 2	Study Group 3	Study Group 4
0 — no respiratory interventions	90	36	28	47
% of group	91.84%	97.30%	89.80%	90.38%
1 — minor respiratory interventions	6	1	0	5
% of group	6.12%	2.70%	10.20%	9.62%
2 — major respiratory interventions	2	0	0	0
% of group	2.04%	0.00%	0.00%	0.00%
General number	98	37	28	52

Table 12. Statistical significance of the parameter of minor respiratory complications in groups according to Pearson/NW after adjusting to include only mothers aged ≥ 35 years

Statistics	Statistical significance of the parameter of minor respiratory complications in groups according to Pearson/NW		
	Chi2	**Df**	**p**
Chi2 Pearsona	3.897165	Df = 3	P = 0.27278
Chi2 NW	5.315896	Df = 3	P = 0.15007

Table 13. Statistical significance of the parameter of major respiratory complications in groups according to Pearson/NW after adjusting to include only mothers aged ≥ 35 years

Statistics	Statistical significance of the parameter of major respiratory complications in groups according to Pearson/NW		
	Chi2	**Df**	**p**
Chi2 Pearson	2.410175	Df = 3	P = 0.49174
Chi2 NW	3.165117	Df = 3	P = 0.36686

In Group 1 it was not possible to obtain data about respiratory complications of the newborn in one case.

When comparing the groups for respiratory complications in relation to subjects aged ≥ 35 years, no statistical differences were noted (Tab. 11). However, a similar pattern to that of the whole group of 368 mothers and newborns was observed, i.e., a higher number of complications in Group 1 compared to Group 2 (Tab. 10).

Results summary

The groups differ in terms of the age of the mother. The average age of our study group of mothers undergoing *in vitro* fertilization was older than the general population of women giving birth in Poland; and the mean age of the whole group was 33.6 years. Group 1 is older, with a mean age of 35.4 years (or a median of 35.5 years), also with highest maximum of the mother's age parameter (48 years). Group 2 is comparable in terms of maternal age to Group 4. In the variable of the mean of weeks of gestation, Group 2 was the least mature compared to groups 1 and 3.

In our analysis of the Apgar scores and respiratory complications data, we observed that Group 2 (pregnancies ending before 39 weeks of gestation) showed results in the birth status of the newborns in relation to the other groups. The rest of the groups showed poorer results in Apgar scores in following minutes, but without statistical significance. The number of respiratory complications (respiratory interventions) was also noticeably lower in study Group 2, but again, without statistical significance.

Theoretically, we expected worse neonatal outcome in Group 2. It would be consistent with the generally accepted recommendation that the optimal timing of elective Caesarean section would be after the 39th week of gestation.

We considered the possible causes of the more cases of neonatal outcomes we found in Group 1 compared to Group 2, was the higher mean age of the mothers in Group 1 (median 35.5 years) compared to the rest of the groups (median 34 years in both groups 2 and 4 and 29 in Group 3). Therefore, we reassessed the study groups, this time separating out those women aged ≥ 35 years, which constituted 42.2% of the total study population.

After analyzing the groups with mothers aged ≥ 35 years, Group 2 was older than Group 1. The results in the analysis of the qualitative data of the newborns (Apgar score and respiratory complications) with mothers aged ≥ 35 years show that the pattern of fewer respiratory interventions and less frequent cases of poorer neonatal Apgar scores in Group 2 persists, though again, without statistical significance. The lack of statistical significance may be due to the small number of patients in the group.

DISCUSSION

Differences between our ECS study group and the general population are due to many demographic and obstetric factors, including the age of the patients, a different method of conception than the natural one, and a greater number of possible complications during pregnancy and delivery. Our analysis of neonate parameters according to gestational age at time of delivery aimed to identify the extent to which our findings may provide guidance for the planning and timing of cesarean sections in order to minimize the risks to newborn children.

Since pregnancy after IVF is considered high-risk, patients are offered delivery by caesarean section. Mothers following *in vitro* fertilisation who are older than the general population's average age for pregnancy, have an increased likelihood of being unable to complete vaginal delivery, requiring emergency caesarean section [7].

The generally accepted recommendations [10, 11] regarding the optimal timing for delivery by Caesarean section indicate that better birth outcomes are observed in newborns delivered after 39 weeks of gestation. Studies show that neonates born at this term have a significantly lower incidence of respiratory complications compared with newborns delivered by elective caesarean section before 39 weeks of gestation [10–12]. The recommended timing is also optimal for the mother, as it allows the cesarean section to be performed before the expected physiological delivery, which in most cases begins spontaneously at 40 weeks of gestation.

In the presented study the group of newborns delivered by caesarean section between 37 and 38 weeks of gestation showed fewer respiratory interventions and less frequent cases of poorer neonatal Apgar scores, if we assume that these pregnancies were correctly dated, which is easier in the case of pregnancies resulting from *in vitro* fertilisation, this result contrasts with the 39th weeks of gestation recommendation.

The influence of maternal age was considered as a possible cause, however, after analysing pregnant women aged ≥ 35 years, the same group of ECS before the 39th week of gestation still showed more cases of neonates that had better condition despite the older mean age of the mothers in the groups. We hypothesised that the effects of maternal age on pregnancy may be less important than the effects of *in vitro* fertilisation.

The main limitation of our study was the small number of cases included, which could influence the significance of statistical differences in some variables.

According to the literature review that we undertook, we believe our study is the first retrospective study to analyse the timing of pregnancy completion following *in vitro* fertilisation with the generally accepted recommendation to perform ECS after 39 weeks of gestation.

CONCLUSIONS

We observed better neonatal outcomes for those delivered by ECS prior to the 39th gestational week. However, the possible causes are unclear as the small number of patients in our analysis of the timing of ECS after *in vitro* fertilisation limited our ability to form strong evidence for earlier delivery. Considering the different characteristics of pregnancy following IVF, further studies should be undertaken to evaluate whether ECS could be planned earlier than indicated in the generally accepted recommendations to deliver after the 39th week of gestation.

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Conflict of interest

The authors have no conflict of interest to declare and nothing to disclose.

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