

The Risk of Birth Asphyxia in Cameroonian Children After *in Vitro* Fertilization: A Retrospective Cohort Study

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Received April 27, 2022; Accepted August 13, 2022; Online Published June 5, 2023

Abstract

Introduction: To demonstrate that birth asphyxia is a risk factor of *in vitro* Fertilization in Cameroon.

Methods: A retrospective cohort study was conducted at the pediatric department of the Hospital Center for Research and Application in Endoscopic Surgery and Human Reproduction (HCRAESHR) in Yaoundé. Every newborn, from *in vitro* fertilization (exposed group) and spontaneous conception (non-exposed group) after a single pregnancy was included and those from multiple pregnancies were excluded. Each group contained 100 newborns that were matched according to the mode of delivery. The data collection lasted 8 months. For that, the birth medical records of the newborns were used and data were reported on individual questionnaires. The absence of cry at birth, an Apgar score <7 at the 5th minute of life, and the concept of neonatal resuscitation including at least the mask ventilation, were the three criteria measured for considering a newborn as having birth asphyxia. A p -value ≤ 0.05 signed the statistical significance of all our results.

Results: The mean maternal age was 40.55 ± 8.35 years in exposed group against 35.72 ± 5.01 years in non-exposed group ($p = 0.000$). The birth asphyxia was significantly predominant in exposed group (35% and 11% respectively, $p = 0.000$), in comparison to non-exposed group. Exposed group had 3.85 times higher risk to have birth asphyxia compared to non-exposed group ($p = 0.001$) while controlling for confounding factors (maternal age, maternal hypertension, prematurity and the sex of the baby).

Conclusion: This study clearly established that *in vitro* fertilization can cause birth asphyxia.

Keywords: *In vitro* fertilization, Asphyxia, Birth, Risk, Cameroon

Introduction

In vitro fertilization is an assisted reproductive technique through which, infertile couples can have a baby. Increasingly used in Africa, it therefore provides a solution to the couple's infertility that represents a real public health issue in Africa.¹ Indeed, infertility is found in 20 to 30% of couples in Cameroon.²

Several authors have conducted studies based on this technique around the world. In Africa, very few of them, were interested about the relationship between birth asphyxia and that method of procreation. There were Ezechi OC. Et al., in Nigeria in 2008³ and Traore SO. et al., in Mali in 2019,⁴ who respectively identified poor Apgar score (less than 7) in 5.8% of newborns at the first minute and in 10.61% of newborns (at the fifth

minute) from women on assisted reproductive techniques including *in vitro* fertilization.

In Cameroon, no study on the risk of birth asphyxia after *in vitro* fertilization (IVF) has been carried out until now, hence was the interest of this retrospective study, carried out at the pediatric department of the Hospital Center for Research and Application in Endoscopic Surgery and Human Reproduction (HCRAESHR) in Yaoundé, Cameroon. Its major objectives were to determine the prevalence of birth asphyxia in newborns from IVF compared to those from spontaneous conception (that without any medical assistance), and to demonstrate that *in vitro* fertilization is a risk factor of birth asphyxia.

Materials and Methods

Study Design-duration and Place of the Study

A retrospective cohort study was conducted during a period of 8 months, from February to September 2021. It was realized at the pediatric department of the Hospital Center for Research and Application in Endoscopic Surgery and Human Reproduction (HCRAESHR) in Yaoundé, Cameroon. It is a public administrative establishment responsible for guaranteeing women, the best medically assisted reproductive conditions. Additionally, they provide high-level care in obstetric gynecology and at the same time, conducting research into endoscopy and human reproduction. The hospital is made up of a maternity, six labor and delivery rooms, a pediatric department including neonatology, six operating rooms for caesarean sections or caesarean deliveries, gynecological surgeries, embryo retrieval, freezing sections and *in vitro* fertilizations. In this hospital, all pregnancies from IVF, without exception, deliver by caesarean. The hospital began offering IVF services in 2015. They realized around 200 cases of IVF per year covering each of the 4 trimesters. From that period until October 2021, around 280 babies were born at the facility through the technique that is around 40 babies born from IVF per year. That is the only assisted reproductive techniques used at that center. During the IVF procedure, frozen/thawed or fresh embryos were used after stimulation process with hormones based on progesterone or oestrogen.

Participants-research Group

The sample size was calculated by using the formula from Serhier Z et al.,⁵ for observational studies and a total sample size of 200 participants was obtained. Were included in our study, all newborns from a single pregnancy after spontaneous conception and after IVF. All newborns from multiple pregnancies were excluded. The sample size was divided into two groups according to the realization of IVF, the exposure factor. The two groups were the exposed group made up of 100 newborns born from a single pregnancy after IVF and the non-exposed group formed of 100 newborns born from a single spontaneous pregnancy at HCRAESHR. During the data collection, the 2 groups were matched according to the mode of delivery with a matching coefficient equal to 1.

Procedure

Data were randomly collected, using hard copies of the birth medical records of the newborns, stored in pediatric department of that hospital. Those data reported on a structured questionnaire, were about IVF realization, Apgar score, the cry at birth, resuscitation, types of resuscitation, delivery mode, gender, maternal parity, abortion, gestational age, and diseases in pregnancy like hypertension and diabetes. The diagnosis of birth asphyxia was based only on 3 clinical criteria or measured indicators, namely the cry at birth, an Apgar score at the 5th minute of life, and the concept of neonatal resuscitation including at least the mask ventilation. Therefore, all newborns with an Apgar score less than 7 at the fifth minute with no cry at birth and who received at least the mask ventilation were considered as having a birth asphyxia.⁶ The Apgar score examines the breathing effort, heart rate, muscle tone, reflexes and skin color of the baby at birth; where each category is scored with 0, 1 or 2 depending on the observed condition.

Statistical Analysis

The collected data were entered and analysed using SPSS (statistical package of social science) software version 23.0 and Excel 2013 for windows version 13.0. Frequency tables were generated and comparisons between the two groups were done using Chi square test, t Student test, and one-way ANOVA (analysis of variance). The relative risk was calculated to highlight the risk of the occurrence of birth asphyxia in newborns after IVF, both without and with consideration of the effects of confounding factors like the sex of baby, the maternal age, the gestational age and the maternal disease in pregnancy such as hypertension. The statistical significance was fixed at $p \leq 0.05$ with a 95% confidence interval and an error of 5%. The outcomes identified as significant at univariate analysis (with a p -value ≤ 0.2) were subjected to generalized linear models using binomial probability distribution while including potential confounding factors. All variables without a significant result ($p \leq 0.05$) were removed and the model was repeated until only all the significant risk factors of birth asphyxia remained.

Ethics

The research was conducted in accordance with the Helsinki Declaration. Ethical clearances were obtained

from ethical committee of the Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan, and of that of the University of Yaoundé 1 in Cameroon. (Ethical number: UI/EC/20/0473).

Results

Population-socio-demographic Characteristics

All the participants were Cameroonian. The two groups were homogeneous with regard to their sex: 40 males and 60 females in each group ($p = 1$).

Maternal Family History

Mothers of newborns conceived after IVF were significantly older at conception than those of newborns spontaneously conceived (40.55 ± 8.35 and 35.72 ± 5.01 years, respectively with $p = 0.000$) (Table 1).

Moreover, the prevalences of primiparity and abortion were significantly predominant in mothers of the exposed group compared to those of the non-exposed group (20 % and 7% with $p = 0.007$ for primiparity and 71% and 43% with $p = 0.000$ for abortion). In contrast, the prevalence of disease in pregnancy were homogeneous in two groups. They were arterial hypertension at 12%, diabetes at 7%, hepatitis B at 4 %, hepatitis C at 3 %, Sickle cells disease at 5% and acquired immune deficiency

syndrome (AIDS) at 1% ($p = 1$).

Mode of Delivery

Newborns in the two groups were all born via cesarean section. In the exposed group, the cesarean was indicated for precious pregnancies due to IVF (infertility). In the non-exposed group, as indications of cesarean, there were 26% of acute fetal distress, 21% of double scar on uterus, 17% of contracted pelvis, 3% of uterine rupture, 8% of prolonged labor, and 4% of umbilical cord prolapse. There were also 10 % of breech presentation, 3% of placenta praevia, 4% of pre-eclampsia and 4% of polymyomatous uterus.

Birth Asphyxia

The birth asphyxia was significantly predominant in newborns conceived after IVF in comparison to those conceived spontaneously (35% and 11% respectively with $p = 0.000$). In fact, those newborns in the exposed group had 4.36 times higher risk to have asphyxia at birth than those of the non-exposed group ($p = 0.000$) (Table 2).

And, when controlling for the potential confounding factors such as their sex, the gestational age, the maternal age at conception, maternal diseases in pregnancy like hypertension, that risk significantly changed into 3.85 ($p = 0.001$) (Table 3).

Table 1. Mean Maternal Age at Conception in Two Groups

Variable	Mean \pm standard Deviation		95% Confidence Interval		Range (min-max)		P-value
	EG	NEG	EG	NEG	EG	NEG	
Maternal age at conception (years)	40.55 \pm 8.35	35.72 \pm 5.01	38.89-42.21	34.73-36.71	26-61	23-49	0.000

EG: Exposed group; NEG: Non-exposed group; Min: Minimum; Max: Maximum.

Table 2. Repartition of the Birth Asphyxia among the Two Groups and its Crude Relative Risk per Groups.

Birth asphyxia	EG: F(RF)	NEG: F(RF)	Crude RR [95% CI]	p-value
Yes	35 (35%)	11(11%)	4.36 [2.06-9.21]	0.000
No	65 (65%)	89 (89%)	0.23 [0.11-0.49]	0.000
Total	100%	100 (%)		

EG: Exposed group; NEG: Non-exposed group; F: Frequency; RF: Relative frequency; RR: Relative risk; CI: Confidence interval.

Table 3. Adjusted Relative Risk (RR), Predicting Birth Asphyxia by Selected Variables (F = 200)

Birth asphyxia	Yes (F= 46)	No (F= 154)	Crude RR (95% CI)	Adjusted RR (95% CI)	B	P-value
IVF						
Yes	35	65	4.36 [2.06-9.21]	3.85 [1.75-8.46]	1.35	0.001
No	11	89	Ref	Ref		
Sex						
Male	25	55	2.14[1.1-4.18]	2.74 [1.31-5.74]	1.01	0.008
Female	21	99	Ref	Ref		
Gestational age						
<37 weeks	11	14	3.14 [1.31-7.52]	2.67 [1.01-7.02]	0.98	0.047
\geq 37 weeks	35	140	Ref	Ref		

F: Frequency; Ref: Reference; CI: Confidence interval; RR: Relative risk.

Discussion

Findings and Interpretations

Maternal Age

Mothers who conceived after IVF were aged on average 40.55 years old and the one who spontaneously conceived were aged on average 35.72 years old. Maternal age was significantly predominant in the exposed group compared to the unexposed group ($p = 0.000$).

This is explained by the fact that, from the age of 40 years old, the fertility rate of Cameroonian women tends to be at its lowest, almost close to zero, that is equal to 0.02.⁷ Consequently, this increases the risk of infertility among these women, pushing them more and more to access medically assisted procreation techniques such as IVF.

The results of Ezechi et al., carried out in Nigeria in 2008,³ are similar to ours, reporting a similar predominant age in mothers who have undergone IVF compared to those who conceived naturally. They reported a significant difference of 6 years between these two groups.

Previous Maternal Pregnancies

We obtained a significant predominance of maternal primiparity and abortion in the exposed group compared to those of the unexposed group. (20% and 71% with $p = 0.007$ and 7% and 43% with $p = 0.000$, respectively).

The underlying explanation stems from the fact that from the age of 40, there is an accelerated decline in the production of quality ovum.⁸ This leads to the increasing formation of abnormal ova called aneuploid ova,⁹ which would be unable to be fertilized because of the chromosomal abnormalities they contain and even if there is fertilization, the resulting embryo carrying the abnormality would cause abortions.⁹ This is one of the reasons why the mothers of the exposed group, being older, are those who have had the most abortions in the past or the most likely to have never conceived before.

Our results agree with those of Ezechi et al., carried out in Nigeria, in 2008,³ which identified a significant abortions predominance of 22% in mothers of newborns born from ART like IVF compared with 2.4% in those of newborns born after spontaneous conception. On the contrary, the results on the primiparity of Traoré SO et al., carried out in Mali in 2019,⁴ disagreed our results, revealing an equal and non-significant primiparity prevalence in the two

groups of 49.78%. This could be because, Traore SO et al., in their study, matched the two groups according to maternal parity.

Birth Asphyxia

We got a significant predominance of birth asphyxia in newborns conceived after IVF compared to those conceived spontaneously (35% and 11% respectively with $p = 0.000$). Indeed, others researchers have obtained results similar to ours, while evaluating the risk of birth asphyxia in newborns from IVF.^{4,13-16}

In fact, the mechanisms by which IVF would cause birth asphyxia are not well known. According to some authors, ovarian stimulation performed during IVF, would cause hormonal changes with early onset of the luteal phase.¹⁰ The latter, characterized by premature thickening of the endometrium, rich in new vessels,¹¹ would lead to uterine vascularization disorders.^{10,11} This would result in the appearance of uterine hypoxia that is a risk factor of asphyxia at birth.¹²

On the contrary, very few studies have shown a prevalence of birth asphyxia rather in spontaneously conceived births compared to those conceived after IVF.^{17,18} According to these authors, this prevalence would come from the causes of female infertility and would not be related to the IVF technique itself.^{17,18}

Furthermore, it is known that criteria such as the sex of the newborn, the maternal age at conception, some disease in pregnancy like hypertension, diabetes, infectious diseases, and the prematurity may expose the newborn to birth asphyxia,¹² but in our study, only the sex of the baby and the gestational age, were significantly associated with birth asphyxia. Therefore, we controlled for those confounding factors and got a significant risk of 3.85 of being born with asphyxia after the use of IVF ($p = 0.001$) than from spontaneous conception.

These findings are actually similar to those of Hayashi et al., realized in Japan, in 2012,¹⁴ who demonstrated that, newborns from IVF significantly have 1.18 times higher risk (with a 95% CI: 0.93-1.49) to have a birth asphyxia comparing to those spontaneously conceived while controlling the effects of similar confounders such as maternal diseases in pregnancy (eclampsia, hypertension), gestational age, birth weight, type of delivery. Besides, the findings of Marino JL et al., carried out in Australia in 2014,¹³ highlighted a significant adjusted odd ratio of 1.59 with a 95% CI:

0.85-2.97 and 1.38 with 95% CI: 0.7-2.19 (respectively with frozen and fresh embryo cycles) of having birth asphyxia after IVF. Here the authors used the same confounding factors than ours notably the gestational age, the maternal age, parity and the sex of the baby.

However, some studies found that newborns from IVF are protective from birth asphyxia.^{15,16} This might be because the authors used different confounding factors such as the ethnicity and the thyroid disease that are not known in the literature as exposing newborns to birth asphyxia.

Strengths and Weaknesses

The use of *in vitro* fertilization as an exposure factor in this retrospective cohort study constitutes one of the strengths of our study. In fact, unlike some studies where the authors used several types of procreation techniques and could not finally distinguish between the effects of each of them,¹⁴⁻¹⁶ there was no risk of confusion about the assisted reproductive techniques used. The other strength is due to the fact that, in the same line of some authors,^{13,14} we computed a multivariate analysis taking into consideration, the effect of some known risk factors of birth asphyxia such as the prematurity, the maternal age, the sex of baby, some maternal disease like the hypertension, all this making our results more reliable and accurate.

On the opposite, as a limitation, we used only a clinical diagnosis of birth asphyxia, similar to that of some authors.^{6,19} Indeed, after getting those clinical criteria, there are some other elements like the umbilical cord arterial pH and neurological ultrasound that we shall perform in newborns to completely confirm the existence of asphyxia. But since those criteria are almost not routinely used in Africa and even less in Cameroon, they were not available on the medical records of the newborns. Therefore, we could not include them into our study. Nevertheless, the definition of birth asphyxia states in our study seems to be more precise than those of Ensing et al.,¹⁵ who considered the Apgar score less than 7 at the 5th minute, as unique component of birth asphyxia. Besides, we used a reduced sample size due to the low success rate of *in vitro* fertilization in Cameroon, associated with the resulting restricted availability of the data at that hospital.

Open Questions and Future Research-recommendations

Throughout our study, we demonstrated that *in vitro*

fertilization is a risk factor of birth asphyxia. Thus, it is important to ask whether all assisted reproduction techniques are involved in the occurrence of birth asphyxia. And if so, which step of *in vitro* fertilization would be the most integrated in this process? Moreover, it also raised concerns about whether birth asphyxia would be the only consequence of the use of these techniques in newborns.

According to the above, our recommendations for future research, are addressed to researchers, so that they carry out larger-scale studies in this direction by scrutinizing as much as possible the consequences of IVF on the health of the newborn, while identifying each time the stage of the process that would be responsible for the occurrence of the detected disease. This is with the aim of improving the effectiveness of this technique in Cameroon and consequently of reducing the failure rate and even the related mortality. We also recommend to the Ministry of Health of Cameroon and to the director of our research hospital, to diversify assisted reproductive techniques within this hospital and then throughout the country; this while simultaneously reviewing its cost downwards. This is to allow a maximum of infertile couples to benefit from it. This would obviously go through the accentuation of awareness campaigns about the infertility of couples.

Conclusion

Our study highlighted a higher frequency of birth asphyxia in newborns resulting from IVF compared to those born spontaneously. In addition, it proved that the risk of being born with asphyxia is higher in newborns resulting from IVF compared to those resulting from spontaneous pregnancies, even under control of the effect of confounding factors. This means that IVF is an indisputable risk factor of birth asphyxia. This raises questions about the methods currently used during the IVF technique in Cameroon; thus pushing us to wonder which stage of IVF would be responsible for this issue. In addition, we wonder whether the damage caused by this technique would be limited only to birth asphyxia or rather whether they would extend to other anomalies. Hence will be the need to carry out in-depth and large-scale studies on this subject; which would help to identify all the health complications of assisted reproductive techniques in newborns, while estimating their risk of occurrence

depending on the type of technique used on one hand and on each step by technique on the other hand.

Conflict of Interest

The authors declare no conflicts of interest.

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