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## Gynecology & Obstetrics

Highlights

Study of Fetomaternal Outcome

Use of Immunoglobulin G Enriched

Reproductive-Age Women in Brazil

Regional Difference in Symptoms Perception

Discovering Thoughts, Inventing Future

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# Is There a Regional Difference in Symptoms Perception Associated with Pre-Menstrual Syndrome? Results from a National Study among Reproductive-Age Women in Brazil

By Adriana Orcesi Pedro, Samantha Belamarques de Oliveira Silva, Maura Gonzaga Lapa, Juliana Dineia Perez Brandao & Vivienne Carduz Castilho

*Universidade Estadual de Campinas*

*Abstract-* *Background:* Evaluate the prevalence, intensity and regional distribution of premenstrual syndrome (PMS) symptoms reported by reproductive age Brazilian women.

*Methods:* An observational and retrospective study was conducted analyzing data of women from the five Brazilian regions. Women aged 20 to 49 years who consulted at private healthcare services filled up a self-reported questionnaire about the prevalence and intensity of somatic and psychoemotional pre-menstrual symptoms.

*Results:* A total of 23104 women stated to have premenstrual symptoms, of which 38.91% (n=8990) reported that these symptoms cause functional impairment.

*Keywords:* *premenstrual syndrome, Brazilian women, regional study, premenstrual severity symptoms, premenstrual prevalence symptoms.*

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*Results:* A total of 23104 women stated to have premenstrual symptoms, of which 38.91% (n=8990) reported that these symptoms cause functional impairment. Among the participants who accepted to answer the detailed symptoms questionnaire (n=5140) a total of 2475 respondents were randomized according to population proportions by Brazilian regions. Among psychoemotional symptoms, irritability was the most prevalent and severe symptom, with 98.5% prevalence and 61.7% severe intensity respectively. Headache was the most prevalent (86.2%) and severe (41%) physical symptom in Brazilian women. For symptom relief, 74.3% of affected women would be willing to take an oral contraceptive pill as a treatment option for PMS.

*Conclusion:* Our study shows a comprehensive overview of the perception of premenstrual symptoms among Brazilian women. Psycoemotional symptoms are more frequent and severe than somatic symptoms regardless of the Brazilian region studied. Also, most of these women would take an oral contraceptive to reduce their premenstrual symptoms and for this reason, health care professionals need to present this option for women suffering from PMS symptoms.

*Keywords: premenstrual syndrome, Brazilian women, regional study, premenstrual severity symptoms, premenstrual prevalence symptoms.*

## I. Background

Premenstrual syndrome (PMS) is a very common dysfunction among women of reproductive age. Approximately 20% to 25% of women experience moderate to severe premenstrual symptoms and about 85% of women experience at least one mild premenstrual symptom[1]. However, few studies reveal the impact of PMS symptoms on quality-of-lifework, family, and social relationships.

There are several different psycho-emotional and physical symptoms associated with PMS as depression, angry outbursts, irritability, anxiety, confusion, social withdrawal, breast tenderness, abdominal bloating, headache and swelling of extremities[2]. These symptoms are cyclic and recurrent and can change in extent and intensity during different menstrual cycles[2]. According to the World Health Organization, "Premenstrual Tension Syndrome" is characterized by certain environmental, metabolic, or behavioral symptoms that occur during the luteal phase of the menstrual cycle, and lead to cyclic emotional, physical, or behavioral symptoms that interfere with an individual's lifestyle[3]. The American College of Obstetrics and Gynecology and the Royal College of Obstetricians and Gynecologists' criteria describe PMS as any number of psychoemotional or physical symptoms and functional impairment is required[4].

Since PMS is a global problem, it has been studied worldwide to understand its effects on daily life[5, 6]. The first global meta-analysis reported the pooled prevalence of PMS at values around 47.8% worldwide, although most of the included studies were heterogeneous, involving several confounding factors within and between studies, and a limited sample size[7]. Some studies suggested that the prevalence of PMS is higher in Latin-American countries when compared to Europe[8].

In Brazil, there are few published studies on the prevalence, symptoms characteristics, and detailed information about the premenstrual syndrome in women of reproductive age. In addition, the correlation with socio-demographic, socioeconomic, and sociocultural conditions of the affected women is not established [9-12]. However, a study in the Brazilian population showed that when using criteria for the diagnosis of PMS, the prevalence of the syndrome was lower than the self-reported [9].

*Corresponding Author α: Department of Gynecology and Obstetrics, Universidade Estadual de Campinas, Campinas, São Paulo, Brazil.*
*e-mail: aopedro@uol.com.br*
*Author σ ρ ω ¥: Libbs Farmacêutica Ltda, Medical Affairs Division, São Paulo, Brazil.*

Therefore, nationwide studies looking at regional differences involving a large sample size among sufferers of PMS are scarce, and new data will contribute to demystifying PMS and help health professionals to assist affected women.

This study aimed to evaluate the prevalence, intensity and regional distribution of PMS symptoms reported by the Brazilian female population and the information generated may help to rethink mechanisms to improve the health and quality of life of PMS suffering women and offer decision-making tools related to the need for early and effective treatment of PMS.

## II. Methods

*a) Study design and sample selection*

It was an observational and retrospective study. All data were collected from a database with information stored by the Market Research Programs (MRP) and anonymized to ensure the data subjects' confidentiality and the study's security and confidentiality.

A self-reported questionnaire was answered by women aged 20 to 49 years from all Brazilian regions: South, Southeast, North, Northeast, and Midwest, between February 2019 and March 2020.The invitation to participate was made through an electronic device (cell phone or tablet). As soon as the woman requested access to the clinic's wireless network, she was invited to participate in the research and received information about the content and purpose of the research. This study was free from a consent form. The duration of the questionnaire filling out was around five to ten minutes.

Next, the participants were categorized as having PMS or not, according to the ACOG diagnostic criteria[2]. To evaluate functional impairment, the participants were asked how much the PMS symptoms disturbed their daily life (not at all, a little, or a lot) and those who answered “a lot” were considered as having a functional impairment.

Those who accepted to participate voluntarily were directed to the questionnaire adapted from the PSST - Premenstrual Symptoms Screening Tool -version validated in Brazil (Annex 1)[13].PSST is a retrospective questionnaire that can be completed during clinical consultation which is well established for PMS symptoms. It has demonstrated high sensitivity (79%) for PMS diagnosis and, in addition, identified women who suffer from severe PMS[14].

A 4-point Likert scale was used to measure the intensity of psychoemotional (irritability, anxiety and tension, decreased interest in routine activities, depression and sadness, overeating, concentration difficulties, emotional instability) and physical(headache, acne and oily skin, edema, weight gain, breast tenderness, exacerbation of immunoallergic conditions) symptoms according to intensity (0 = none; 1 = mild; 2 = moderate; 3 = severe). Also, demographic data of the participants were collected, and they were asked whether they would take oral contraceptives as a treatment option for PMS.

To have representativeness according to regional population, the respondent women were randomly selected according to the population proportions by region, based on the latest published demographic Census (2010)[15]. The study flow chart is represented in Figure 1.

The study protocol was submitted to the Research Ethics Committee under the registration number 33794520.1.0000.8098.

*b) Sample Calculation*

To calculate the sample size, an estimation formula was used for a descriptive study with a categorical qualitative variable[16-18]. In this case, the premenstrual syndrome (PMS) estimate was obtained from the literature[10].The level of significance alpha or type I error was set at 5% (or 95% confidence interval) and the sampling error at 3% (d=0.03). According to the results, a minimum sample of n=1022 was obtained. The program used was SAS (Statistical Analysis System), version 9.4 (SAS Institute Inc, 2002-2012, Cary, NC, USA).

According to the 2010 Demographic Census data, [15] the Brazilian female population aged 20 to 49 years was distributed as follows: 42.4% in the Southeast, 26.9% in the Northeast, 14.1% in the South, 8.9% in the Midwest and 7.7% in the North region. A specific procedure was used for this selection that randomly shuffles and chooses lines among those available in each region, using the SAS statistical software.

*c) Statistical methods*

According to the variables under study, the sample characteristics are shown as frequency tables of categorical variables with absolute (n) and percentage (%) frequency values.

Comparisons among regions concerning the response of each question were analyzed using Pearson's Chi-Square test or Analysis of Variance (ANOVA). If a significant difference was found at 5% in the first test, multiple comparisons were performed so that each region was compared. Bonferroni's correction test was used for multiple comparisons.

The p-value was considered significant at 0.8%, resulting from the significance level of 5% divided by 6.We used Poisson Regression to compare regions regarding the number of moderate or severe symptoms, an appropriate statistical test for numerical data. All analyzes were performed using SAS software version 9.4 and Excel.

## III. Results

A total of 56,948 women responded to the initial questionnaire. Of these, 8,990 were aged between 20 and 49 years and met the diagnostic criteria for PMS (any number of psycho-emotional or physical symptoms with functional impairment). Among them, 5,121 participants agreed to answer a detailed anamnesis about their symptoms, characterizing the target population of the study.

After that, 2,475 respondents were randomized respecting the proportionality of the female population of each state, according to the 2010 census(Table 1).

The mean age of participants was 30.8 ± 7.4 years. Women between 20 and 29 years represented 47.8% of the sample, corresponding to the larger age group. The participants aged between 40 to 49 years represented the lowest proportion of respondents (14.4%).The mean age was higher in the southeast region (31.4, p=0.0003). Among the different Brazilian regions, the proportion of respondents in each age group was uniform (Table 2).

The profile of the participants who did not accept to respond to the questionnaire was similar to participants who accepted to respond, regarding the Brazilian regions and age group. Half of the participants in each profile agreed to answer the questionnaire.

By analyzing the total prevalence of symptoms and the distribution of severe physical symptoms, it was observed no significant differences between the regions of Brazil, except for the lower prevalence of weight gain in the northeast region (Table 3).

Headache was the most prevalent physical symptom (86.2%) in the Brazil average, as well as in the South and Midwest regions, and 41% of the women with headaches presented the symptom with severe intensity. The second most prevalent symptom in the Brazil average was acne and oily skin (85.8%), with 32.3% of severe intensity, followed by edema (85% prevalence, 25.5% with severe intensity). Acne and oily skin were also the most prevalent symptom in the Southeast and Northeast regions. In the North region, edema was the most prevalent physical symptom (Table 3).

Weight gain was the only physical symptom with a statistically significantly lower prevalence in the northeast region compared to other regions of the country (Table 3).

The least prevalent and severe symptom was an exacerbation of immunoallergic conditions (78.8% and 15.4%) respectively (Table 3).

When focusing on the psychoemotional symptoms, the most prevalent symptom in the country was irritability (98.5%) with 61.7% of women presenting the symptom in severe intensity. Anxiety and tension were the second most prevalent psychoemotional symptom in the Brazilian population (98.4%) and 54.2% of the participants presented it in severe intensity (average). The most prevalence of this symptom was observed in the south region. Regarding intensity, it was statistically significant in the northeast and southeast regions. In the South region, both symptoms (irritability / Anxiety and tension) showed the same higher prevalence (99.4%). The third most prevalent symptom in the country was decreased interest in routine activities (94.5%) and 39% of women considered it to be of severe intensity (Table 4).

Overeating was the only symptom was observed with a statistically significant difference between regions for prevalence and intensity.

On average, 74.3% of women with PMS stated they would take contraceptivesas an option for PMS symptoms treatment (Table 5).

## IV. Discussion

Our investigation showed a high prevalence of physical and psychoemotional symptoms in all Brazilian regions, with the average prevalence of these symptoms in Brazil being 83.6% and 94.2%, respectively.

In a study in southern Brazil 1395 women aged 15 to 49 years were evaluated. The main premenstrual physical symptoms found in this study were abdominal discomfort, headache and breast pain. Among the psychoemotional symptoms, the most prevalent were irritability, nervousness and fatigue.[9] In our study the most prevalent physical symptoms were headache (86.2%), acne and oily skin (85.8), and edema (85%) and the psychoemotional symptoms were irritability (98.5%), anxiety and tension (98.4%) and decreased interest in routine activities (94.5%).

In a multicenter Brazilian study that aimed to describe the perspectives and attitudes of Brazilian women toward premenstrual syndrome,1053 women, separated by regions, between 18 and 40 years, lived in 6 Brazilian cities, 1 in each geographic region of the country and the Federal District were interviewed [10]. Results showed that most women (78.1%) stated that PMS is related to emotional symptoms, and 24.3% said that it is related to physical symptoms [10]. The emotional symptoms most frequently mentioned by the participants were nervousness/anxiety, irritability/anger/ aggressiveness and mood swings/crying, whereas the most common physical symptoms were headache, cramps and breast pain, swelling, and tenderness[10]. On the other hand, in our investigation we observed that irritability and anxiety/tension were the most prevalent psychoemotional symptoms.

When evaluating the prevalence of symptoms with severe intensity, our study showed a higher prevalence of psychoemotional symptoms over physical symptoms, reaching 60% for irritability versus 40% for headache, which was the most severe physical symptom.

In a study across several countries, including Brazil, with a total of 7226 women (400–500 women from each country) aged 15-49, it has been reported a higher frequency of physical symptoms, as assessed by severity and number of menstrual cycles affected[6]. In this global study, Brazil was characterized by the second-largest values of severity and duration of symptoms, staying only behind the UK. The high prevalence of severe symptoms observed in our study corroborates these findings. However, when evaluating the global population, among the 5 most prevalent symptoms, 4 were physical[6]. In our study, psychoemotional symptoms were a higher prevalence and severity. It is important to highlight that these data were collected before the pandemic of COVID-19, so these results were not influenced by the psychological effects seen during the pandemic. We continue to collect data during the pandemic, and it will be interesting to compare this issue.

The lower severity of overeating in the northeast region may be related to the lower severity of anxiety and tension during the premenstrual period.

Previously studies showed that among Brazilian women, 52.3% stated that physicians prescribed hormones as a strategy for dealing with premenstrual syndrome, [10] and PMS symptoms severity was inversely associated with oral contraceptive use (emotional symptoms) and better-perceived health (physical symptoms)[19].In our investigation, among respondents who met the diagnostic criteria for PMS (n=2.475), 74.3% would take oral hormonal contraceptives as a treatment option for PMS. This is an important finding since the combined oral contraception for women of reproductive age is one of the effective options used for the treatment of PMS, mainly for women who seek contraception counseling.[20]

The strength of this study includes the use of a questionnaire validated in Brazil that is commonly used for population studies, the large number of women included, and the national scope of the study. In addition, the participating women included in our study were selected in a private healthcare system to minimize bias-related the socioeconomic status of participants. A limitation of this study is that data such as education and family income of the participants were not collected.

## V. Conclusion

Psychoemotional symptoms are more frequent and severe than somatic symptoms. There were a lot of similarities in women's experiences of these symptoms across Brazilian regions. Symptoms had a frequency and intensity regardless of the region, which makes many women states that would be willing to take a contraceptive that reduces TPM symptoms. It is important for healthcare professionals, to make screening symptoms associated with SPM during contraception counseling to choose the most proper option.

*List of abbreviations*

Premenstrual syndrome; MRP: Market Research Programs; PSST: Premenstrual Symptoms Screening Tool

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*Authors contribution*

Adriana O. Pedro contributed to the design, writing and revision of the manuscript; Samantha B. O. Silva contributed to the design, data analysis and wrote the manuscript; Maura G. Lapa contributed to data analysis; Juliana D. P. Brandao contributed to data analysis and wrote the manuscript and Vivienne C. Castilho contributed to the design and revision of the manuscript.

All authors discussed the results and contributed to the final manuscript.

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*Availability of data and materials*

The data generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

*Declarations*

All procedures performed in this research were in accordance with the ethical standards and approved by Research Ethics Committee in all participating sites and was conducted following the ethical standards outlined in the Helsinki Declaration (1983).

*Competing interests*

Adriana O. Pedro has served on advisory boards or has been a consultant for Libbs Farmacêutica, Abott, Achè, Amgen, EMS, Eurofarma, Grumenthal, Mantecorp-Farmasa, and Sanofi. She has also served on the speaker's bureau for Libbs Farmacêutica, Abott, Achè, Amgen, EMS, Eurofarma, Grumenthal, Mantecorp-Farmasa, and Sanofi-Aventis.

Samantha B. de Oliveira, Maura G. Lapa, Juliana D. P. Brandao and Vivienne C. Castilho are employed at Libbs Farmacêutica, Medical Affairs Division.

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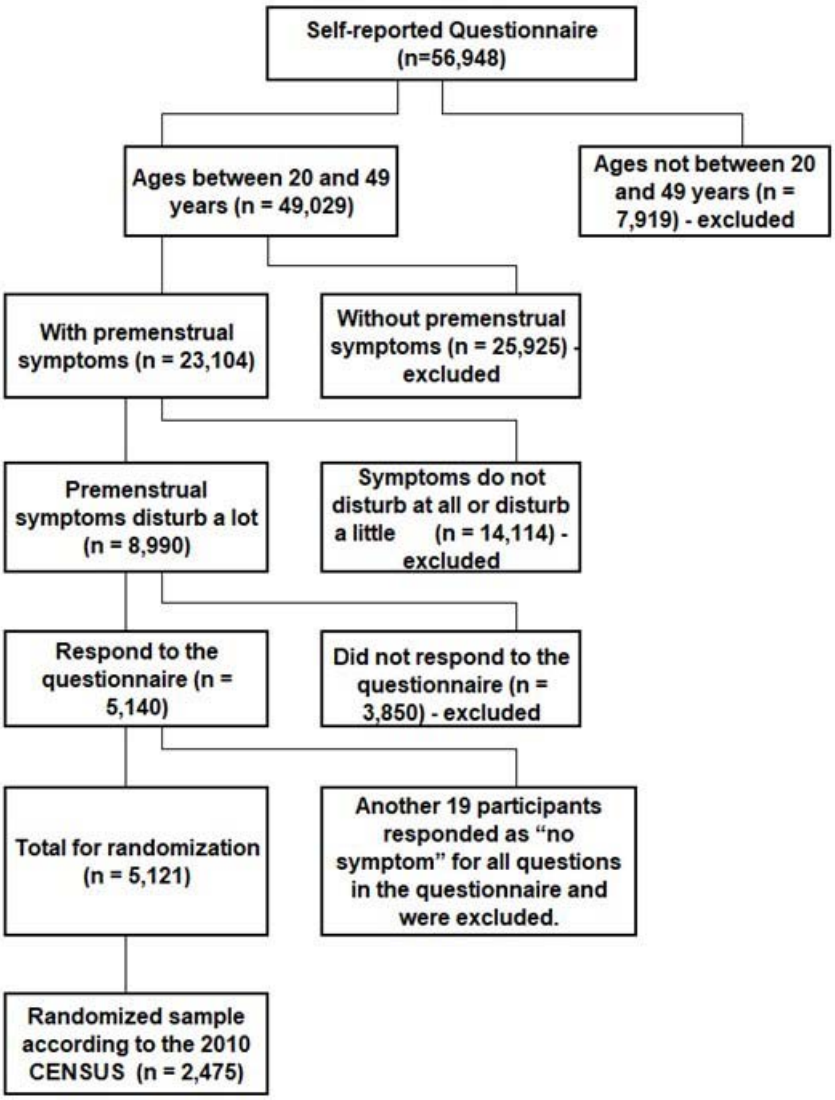


*Figure 1:* Flowchart of participants included in the study (n=2475).

*Table 1:* The number of responses from each region available in the database (Target Population) vs. the number of participants selected after randomization, respecting the proportionality of the female population of each state according to the 2010 Census (Random Selection).

| Region | State | Target Population | | Random selection | |
|---|---|---|---|---|---|
| Midwest | Distrito Federal | 91 | (35.3%) | 79 | (35.7%) |
| | Goiás | 94 | (36.4%) | 79 | (35.7%) |
| | Mato Grosso | 54 | (20.9%) | 46 | (20.8%) |
| | Mato Grosso do Sul | 19 | (7.4%) | 17 | (7.7%) |
| | **Total** | **258** | (100%) | **221** | (100%) |
| North | Amazonas | 114 | (57.6%) | 108 | (56.8%) |
| | Pará | 41 | (20.7%) | 40 | (21.1%) |
| | Tocantins | 43 | (21.7%) | 42 | (22.1%) |
| | **Total** | **198** | (100%) | **190** | (100%) |

| | | | | | |
|---|---|---|---|---|---|
| Northeast | Alagoas | 7 | (1.1%) | 7 | (1.1%) |
| | Bahia | 98 | (14.7%) | 98 | (14.7%) |
| | Ceará | 124 | (18.6%) | 124 | (18.6%) |
| | Maranhão | 38 | (5.7%) | 38 | (5.7%) |
| | Paraíba | 31 | (4.7%) | 31 | (4.7%) |
| | Pernambuco | 218 | (32.7%) | 218 | (32.7%) |
| | Piauí | 124 | (18.6%) | 124 | (18.6%) |
| | Rio Grande do Norte | 20 | (3.0%) | 20 | (3.0%) |
| | Sergipe | 6 | (0.9%) | 6 | (0.9%) |
| | **Total** | **666** | (100%) | **666** | (100%) |
| South | Paraná | 191 | (38.1%) | 133 | (38.2%) |
| | Rio Grande do Sul | 196 | (39.1%) | 135 | (38.8%) |
| | Santa Catarina | 114 | (22.8%) | 80 | (23%) |
| | **Total** | **501** | (100%) | **348** | (100%) |
| Southeast | Espírito Santo | 154 | (4.4%) | 46 | (4,4%) |
| | Minas Gerais | 651 | (18.6%) | 196 | (18.7%) |
| | Rio de Janeiro | 805 | (23%) | 242 | (23%) |
| | São Paulo | 1888 | (54%) | 566 | (53.9%) |
| | **Total** | **3498** | (100%) | **1050** | (100%) |
| Total | | 5121 | | 2475 | |

*Table 2:* Brazilian region by age group in a random sample of the target population. (n=2475)

| **Region of Brazil** | **Midwest (n=221)** | | **North (n=190)** | | **Northeast (n=666)** | | **South (n=348)** | | **Southeast (n=1050)** | | **TOTAL (n=2475)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Profile - n (%)** | | | | | | | | | | | | |
| 20 to 29 years | 107 | (48.4) | 106 | (55.8) | 341 | (51.2) | 168 | (48.3) | 462 | (44.0)* | 1184 | (47.8) |
| 30 to 39 years | 80 | (36.2) | 63 | (33.2) | 247 | (37.1) | 128 | (36.8) | 417 | (39.7) | 935 | (37.8) |
| 40 to 49 years | 34 | (15.4) | 21 | (11.1) | 78 | (11.7) | 52 | (14.9) | 171 | (16.3) | 356 | (14.4) |
| Total of participants | 221 | (100%) | 190 | (100%) | 666 | (100%) | 348 | (100%) | 1050 | (100%) | 2475 | (100%) |
| Mean (S.D.) | 30.7 (7.4) | | 29.8 (7.2) | | 30.2 (7.3) | | 30.5 (7.5) | | 31.4 (7.4) | | 30.8 (7.4) | |
| Median (Min - Max) | 30 (20 - 49) | | 28 (20 - 49) | | 29 (20 - 49) | | 30 (20 - 49) | | 31 (20 - 49) | | 30 (20 - 49) | |
| p (Anova Region * Age) = 0.0043 | p = 0.9641 | | p = 0.0645 | | p = 0.0222 | | p = 0.4165 | | p = 0.0003 | | | |

Multiple comparisons: each region with the rest of country (α for Bonferroni correction = 0.008)

* numbers means statistical significance compared with the others.

*Table 3:* The prevalence and severity of physical symptoms according to Brazilian regions (n=2475).

| Region of Brazil | | Midwest (n=221) | North (n=190) | Northeast (n=666) | South (n=348) | Southeast (n=1050) | TOTAL (n = 2475) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Physical symptoms (%)** | | | | | | | | |
| Headache | Prevalence | 86.8 | 86.3 | 85.7 | 87.6 | 85.9 | 86.2 | p = 0,9253 |
| | Severe intensity | 43.2 | 39.6 | 41.3 | 41.0 | 40.6 | 41.0 | p = 0.9615 |
| Acne and oily skin | Prevalence | 85.1 | 84.2 | 86.2 | 85.1 | 86.3 | 85.8 | p = 0.9209 |
| | Severe intensity | 33.0 | 33.7 | 33.3 | 33.4 | 30.9 | 32.3 | p = 0.8343 |
| Edema | Prevalence | 84.2 | 88.9 | 84.4 | 86.5 | 84.4 | 85.0 | p = 0,4676 |
| | Severe intensity | 23.1 | 29.6 | 22.2 | 24.3 | 27.7 | 25.5 | p = 0.1077 |
| Weight gain * | Prevalence | 84.6 | 81.6 | 79.7* | 85.3 | 85.3 | 83.5 | p = 0.0267* |
| | Severe intensity | 32.6 | 36.1 | 31.5 | 30.0 | 36.7 | 34.0 | p = 0.1298 |
| Breast tenderness | Prevalence | 84.6 | 84.2 | 81.2 | 82.8 | 82.1 | 82.3 | p = 0.7556 |
| | Severe intensity | 30.8 | 25.9 | 24.8 | 22.0 | 25.1 | 25.1 | p = 0.3888 |
| Exacerbation of immunoallergic conditions | Prevalence | 79.6 | 82.1 | 77.4 | 79.6 | 78.6 | 78.8 | p = 0,6934 |
| | Severe intensity | 19.9 | 10.3 | 15.5 | 14.8 | 15.5 | 15.4 | p = 0.2006 |

* numbers means statistical significance compared with the others.

*Table 4:* Psychoemotional symptoms according to prevalence and severity for different regions of Brazil (n=2475).

| Region of Brazil | | Midwest (n=221) | North (n=190) | Northeast (n=666) | South (n=348) | Southeast (n=1050) | TOTAL (n=2475) | p-value |
|---|---|---|---|---|---|---|---|---|
| **Psycho-emotional symptoms (%)** | | | | | | | | |
| Irritability | Prevalence | 98.6 | 97.7 | 97.6 | 99.4 | 99.0 | 98.5 | p = 0.0975 |
| | Severe intensity | 64.7 | 64.5 | 58.9 | 58.7 | 63.3 | 61.7 | p = 0.1935 |
| Anxiety and tension* | Prevalence | 97.7 | 96.3 | 98.0 | 99.4 | 98.8 | 98.4 | p = 0.0501 |
| | Severe intensity | 58.3 | 50.8 | 50.4 | 50.0 | 57.66 * | 54.2 | p = 0.0085 * |
| Decreased interest in routine | Prevalence | 95.5 | 93.2 | 94.9 | 94.0 | 94.6 | 94.5 | p = 0.8327 |
| | Severe intensity | 39.8 | 35.6 | 39.6 | 38.5 | 39.2 | 39.0 | p = 0.9027 |
| Depression and sadness | Prevalence | 96.4 | 92.6 | 93.7 | 95.1 | 94.6 | 94.4 | p = 0.4339 |
| | Severe intensity | 45.5 | 38.1 | 41.5 | 44.7 | 45.6 | 43.8 | p = 0.2495 |
| Overeating * | Prevalence | 91.0 | 89.5 | 89,2* | 94.3 * | 92.5 | 91.5 | p = 0.0347 * |
| | Severe intensity | 47.8 | 37.6 * | 42.5 * | 52.7 * | 50.6 * | 47.5 | p < 0.001 * |
| Concentration difficulties | Prevalence | 91.4 | 92.1 | 92.9 | 91.4 | 89.9 | 91.2 | p = 0.2926 |
| | Severe intensity | 21.8 | 23.4 | 26.5 | 23.6 | 23.3 | 24.1 | p = 0.5664 |
| Emotional instability | Prevalence | 93.2 | 93.2 | 90.4 | 90.8 | 90.7 | 91.0 | p = 0.5801 |
| | Severe intensity | 30.6 | 32.2 | 30.1 | 30.1 | 33.6 | 31.8 | p = 0.5795 |

* numbers means statistical significance compared with the others.

*Table 5:* Percentage of women willing to take an oral hormonal contraceptive as an option treatment of PMS treatment according to the regions (n=2475).

| Region of Brazil | Midwest (n=221) | North (n=190) | Northeast (n=666) | South (n=348) | Southeast (n=1050) | TOTAL (n=2475) |
|---|---|---|---|---|---|---|
| Willing to take the contraceptive - n (%) | | | | | | |
| No | 57 (25,8%) | 41 (21,6%) | 159 (23,9%) | 99 (28,4%) | 280 (26,7%) | 636 (25,7%) |
| Yes | 164 (74,2%) | 149 (78,4%) | 507 (76,1%) | 249 (71,6%) | 770 (73,3%) | 1839 (74,3%) |
| Total responders | 221 (100%) | 190 (100%) | 666 (100%) | 348 (100%) | 1050 (100%) | 2475 (100%) |

p (Chi-Square for Region*Willing) = 0.315

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# Use of Immunoglobulin G Enriched with IGM+IGA in Primigestant with Septic Shock: Case Report

By Jaime A. Machado-Bernal, María C. Espinosa-González, Hernán L. Valle-Calderón & Belkis X. Quant-Vergara

*University of Colombo*

*Abstract-* Sepsis is a condition that occurs when the body produces an unbalanced immune response to an infection. Septic shock is the most serious manifestation of this infection, which increases with aggravation of maternal and perinatal morbidity and mortality. Within the pharmacological therapeutic options, the cornerstone of this entity is broad-spectrum antibiotic therapy; however, there are other drugs that can be used as adjuvants in the context of sepsis and among them are immunoglobulins. Currently there is little scientific evidence about the use of immunoglobulins in pregnant patients and in Colombia there is only one case report published so far. The objective of this patient report is to present the case of a primipregnant woman with a pregnancy of 16.3 weeks diagnosed with septic shock who was administered immunoglobulin G enriched with IgM + IgA, which had an excellent response to the established treatment and satisfactory evolution. without presenting maternal or fetal adverse effects to the drug.

*Keywords: sepsis. septic shock. pregnancy. infectious complications of pregnancy. intensive care units. intravenous immunoglobulins.*

*GJMR-E Classification: DDC Code: 616.94 LCC Code: RC182.S4*

*Strictly as per the compliance and regulations of:*

# Use of Immunoglobulin G Enriched with IGM+IGA in Primigestant with Septic Shock: Case Report

## Uso De Inmunoglobulina G Enriquecida Con IGM+IGA En Primigestante Con Choque Séptico: Reporte De Caso

Jaime A. Machado-Bernal [α], María C. Espinosa-González [σ], Hernán L. Valle-Calderón [ρ] & Belkis X. Quant-Vergara [ω]

*Abstract-* **Sepsis is a condition that occurs when the body produces an unbalanced immune response to an infection. Septic shock is the most serious manifestation of this infection, which increases with aggravation of maternal and perinatal morbidity and mortality. Within the pharmacological therapeutic options, the cornerstone of this entity is broad-spectrum antibiotic therapy; however, there are other drugs that can be used as adjuvants in the context of sepsis and among them are immunoglobulins. Currently there is little scientific evidence about the use of immunoglobulins in pregnant patients and in Colombia there is only one case report published so far. The objective of this patient report is to present the case of a primipregnant woman with a pregnancy of 16.3 weeks diagnosed with septic shock who was administered immunoglobulin G enriched with IgM + IgA, which had an excellent response to the established treatment and satisfactory evolution. without presenting maternal or fetal adverse effects to the drug. It is concluded that this drug could be used in pregnant patients as adjuvant therapy in this population.**

*Keywords: sepsis. septic shock. pregnancy. infectious complications of pregnancy. intensive care units. intravenous immunoglobulins.*

## I. Introduction

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection according to the Third Internal Consensus Definitions for Sepsis and Septic Shock of the Task Force[1]. Sepsis and septic shock are major health problems that affect millions of people worldwide each year[2].

Regarding sepsis in the obstetric population, its incidence is different in developed and underdeveloped countries, varying from 0.96 to 7.04 per 1,000 women aged between 15 and 49 years. As for the estimated global mortality rates, they ranged from 0.01 to 28.46 per 100,000 women between 15 and 49 years of age[3,4]. Regarding national figures and based on the report made in 2021 by the National Institute of Health of Colombia, sepsis related to pregnancy corresponded to 3%[5]. According to the World Health Organization, sepsis is the third leading cause of maternal death in the world[6]. The main non-obstetric conditions associated with sepsis in pregnant women are urinary tract infections; however, in countries like Colombia, it is important to consider tropical infectious diseases such as malaria, which could be a pathology to take into account originating from sepsis[7].

The pathophysiology of maternal sepsis is based on an excessive inflammatory response which includes extravasation of albumin and fluid, with subsequent intravascular hypovolemia. Likewise, the release of cytokines leads to a decrease in systemic vascularization, resistance and an increase in cardiac output[8]. During normal pregnancy, the human decidua contains high numbers of immune cells such as macrophages, natural killer (NK) cells, and regulatory T (Treg) cells. Consequently, the presence of immune cells at the implantation site is not associated with a "foreign body" response (the fetus), on the contrary, they have been attracted to facilitate and protect pregnancy[9].

Regarding immunoglobulins, the immunoglobulin formulation enriched with IgM and IgA (12% IgM, 12% IgA and 76% IgG). Relevant mechanisms of action of IgM- and IgA-enriched immunoglobulins include opsonization and phagocytosis of causative pathogens[10], neutralization of virulence factors, including bacterial endotoxins and exotoxins, as well as immunomodulation through interaction with complement factors and prevention of proinflammatory responses. Immunoglobulins have also been shown to down-regulate IL-2 production, resulting in significant inhibition of the proliferative response of human T lymphocytes in vitro, as well as in peripheral blood mononuclear cells stimulated with IL-2. lectin, In addition, in vitro and in vivo models have shown an increase in IL-10 after administration of IgM- and IgA-enriched immunoglobulins.

*Author α σ: Physician. Resident of Gynecology and Obstetrics of II year. Universidad Libre. Barranquilla. Atlantico. Colombia.*
*e-mail: janama1996@gmail.com*
*Author ρ: Physician. Specialist in gynecology and obstetrics. Hospital Camino Universitario Adelita de Char. Obstetrics and Gynecology Coordinator. Postgraduate teacher of Gynecology and Obstetrics. Universidad Libre. Barranquilla. Atlantico. Colombia.*
*Author ω: Medical. Specialist in gynecology and obstetrics. Hospital Camino Universitario Adelita de Char. Barranquilla. Atlantico. Colombia.*

Regarding diagnosis, an obstetric modification of qSOFA was proposed by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[11] and includes: systolic blood pressure ≤ 90 mm Hg, respiratory rate > 25/min, and altered mental status. These SOMANZ guidelines also include changes in laboratory values when applying the SOFA score in pregnancy, as shown in Table 1.

*Table 1:* Sequence for the evaluation of modified organ failure in obstetrics (omSOFA) [11]

| omSOFA variables. | Points | 0 | 1 | 2 |
|---|---|---|---|---|
| PaO2/FiO2 respiration. | | > 400 | 300-400 | < 300 |
| Platelets | | ≥ 150.000/mm3 | 100.000 – 150.000/mm3 | < 100.000/mm3 |
| Bilirrubins (mg/dL) | | ≤ 1.17 | 1.17 – 1.87 | > 1.87 |
| Mean arterial pressure (MAP) | | PAM ≥ 70 | < 70 | Need for vasopressor to maintain MAP |
| Consciousness state | | Alert | Wake up to verbal encouragement | Arouses only to physical stimulation or pain |
| Serum creatinine(mg/dL) | | < 1.0 | 1.0 – 1.36 | > 1.36 |

Sepsis in the pregnant population is a serious entity that has both short-term and long-term maternal and perinatal complications; such complications can even lead to maternal or neonatal death. Important neonatal complications include: preterm delivery, neonatal sepsis, chronic lung disease, brain injury secondary to maternal infection, and neurodevelopmental disorders[12].

Ideally, the indication of this medication is recommended up to 24 hours after the diagnosis of sepsis is made, however, it may be indicated when there has been no satisfactory evolution after 3 days of initial antibiotic therapy[13]. However, there is little evidence to support it.

Until now, only one published case report is known in Colombia in the context of an obstetric patient with a diagnosis of sepsis who was administered immunoglobulin G enriched with IgM and IgA with adequate clinical evolution, for which, taking into account the above, the objective of this report is to publicize and promote a new therapeutic option in obstetric patients with sepsis and inadequate response to conventional management.

## II. Case Reporte

We present a 20-year-old patient, primiparous, with a pregnancy of 16.3 weeks by ultrasound between weeks 11-14, without significant pathological or surgical history, obstetric history: first pregnancy, without any prenatal control, or paraclinical tests to date, never cytology had been performed, she did not remember the date of her last period, menarche at 13 years of age; history of immunization single dose of vaccine for COVID-19 (Astrazeneca 1 dose - did not remember the date), who was admitted to the emergency department of a low-complexity center (Hospital PASO La Manga) due to clinical symptoms of approximately 3 days of evolution, sudden onset, characterized by abdominal pain 10/10 according to the visual analog scale, located in the hypogastrium, radiating to the bilateral lumbar region and the right thigh associated with dysuria, bladder tenesmus and dizziness and nausea, without emetic episodes. Refers outpatient treatment with cephradine 500mg, 1 tablet orally every 8 hours for 2 days without improvement. On admission physical examination, vital signs were stable but febrile (blood pressure 100/60mmHg, heart rate 86bpm, respiratory rate 18rpm, ambient oxygen saturation 99%, temperature 38°C); abdomen slightly painful on palpation in the hypogastrium and positive bilateral fist percussion, without vaginal leakage; It is managed in the emergency room with saline solution 500CC in bolus and continues at 80CC/hr, acetaminophen 2 tablets orally. Paraclinical tests were performed: normal blood cell count, urinalysis suggestive of urinary tract infection (bacteria ++, leukocytes 15xc, positive nitrites), negative acute phase reactants; Therefore, they consider that they have a urinary tract infection and initiate referral procedures to be managed and assessed by the gynecology and obstetrics service at Camino Universitario Distrital Adelita de Char.Upon admission to this center, vital signs were reported within normal parameters (blood pressure: 110/60 mmHg, heart rate 80 bpm, respiratory rate 18 rpm, oxygen saturation 98%, temperature 37°C), on physical examination there were no signs of dehydration, abdominal pain in the hypogastrium of lesser intensity, without signs of peritoneal irritation, in the gynecological examination abundant non-fetid leukorrhea was evidenced, closed cervix and pain on mobilization of the cervix and on mobilization of the adnexa. A diagnosis of pyelonephritis associated with bacterial vaginosis was considered clinically and intravenous antibiotic management with cephalothin 1 gram IV every 6 hours was continued for 2 more days during said hospitalization. Subsequently, due to adequate clinical evolution and negative urine culture report at 48 hours (probably biased by antibiotic treatment previously

received by the patient), she was discharged with cephradine 500mg, 1 tablet orally every 8 hours for urinary tract infection and metronidazole in ovules for the management of bacterial vaginosis, 1 ovule each day until completing 7 days with order of control urine culture 5 days after completion of antibiotic treatment.

Patient who is readmitted approximately 3 weeks later, with a pregnancy of 20.1 weeks, reporting the same symptoms of admission in the previous hospitalization, also comments that the outpatient treatment was not carried out adequately and the ordered control urine culture was not performed. He was admitted to the observation/emergency department with stable vital signs (blood pressure: 100/65 mmHg, heart rate 96 bpm, respiratory rate 18 bpm, oxygen saturation 98%, temperature 37.3°C, normal fetocardia 140 bpm), without omSOFA criteria in that moment; Management was started with bolus saline solution and after maintenance, hyoscine ampule 20mg intravenously in a single dose, analgesic treatment with acetaminophen 1 gram orally and laboratories were requested again: complete blood cell count, partial urine count and acute phase reactants, HIV and serology for syphilis.Paraclinical tests were performed that same day, which were reported as follows (Table 2):

*Table 2:* Paraclinical

| PATIENT VALUES | REFERENCE VALUES |
|---|---|
| HIV: NEGATIVE. | HIV: NEGATIVE. |
| TREPONEMIC TEST: NON-REACTIVE | TREPONEMIC TEST: NON-REACTIVE |
| COMPLETE BLOOD COUNT: WBC: 13000, N: 78%, HB: 10, HTO: 33, PLT: 144.000. | COMPLETE BLOOD COUNT: WBC: 10.000-15.000, N: 60% - 80%, HB: 12 – 15, HTO: 38 – 48, PLT: 150.000 – 450.000 |
| CRP: 1.34 | CRP: 1 – 3. |
| UROANALYSIS: NITRITOS NEGATIVOS, LEUCOCITOS INCONTABLES, BACTERIAS ++. | UROANALYSIS: NITRITOS: NEGATIVOS, LEUCOCITOS: 0-5XC, BACTERIAS ESCASAS. |

*HIV: human immunodeficiency virus, WBC: White blood cells, N: neutrophils, HB: hemoglobin, HTO: hematocrit, PLT: platelets. CRP: C-reactive protein.*

Pyelonephritis was again documented, for which the patient was hospitalized to start intravenous in-hospital antibiotic management (ampicillin/sulbactam, 3 g IV every 6 hours) and a urine culture was requested, renal and urinary tract ultrasound was performed, reporting a finding of bilateral hydronephrosis. grade II without findings of renal lithiasis or other alterations (figure 1). Patient who remained 4 days of hospitalization under antibiotic treatment mentioned above with stable evolution, however, on the 5th day of hospitalization he presented abrupt torpid evolution of his clinical picture with blood pressure figures with a tendency to hypotension, tachypnea, tachycardia (blood pressure 80/50mmHg, respiratory rate 28rpm, heart rate 112lpm, wakes up to verbal stimulation) (omSOFA: 2pts), then considering a diagnosis of sepsis of urinary origin, for which it was indicated to stagger antibiotic treatment to piperacillin/tazobactam at a dose of 4.5gr IV every 8 hours, a bolus of 2000cc (30cc/kg) was administered and basal fluids were continued at 100cc/hr; extension laboratories for sepsis were requested (Table 3) and transfer to the intensive care unit for comprehensive management was indicated.

*Table 3:* Paraclinical

| |
|---|
| TP: 13. INR: 1.02. TPT: 29, 8. ALT: 13, 8. ASAT: 20, 9. |
| CR: 0,8. LDH. 196. BUN: 14. LACTATO: 1,9. |
| HEMOGRAMA: WBC: 13000, N: 78%, HB: 7.9, HTO: 24, PLT: 53.000 |
| PCR: 0.04 |
| CL: 105. K: 3,1. NA: 137. |

PT: prothrombin time, INR: international normalized ratio, PTT: partial thromboplastin time, CR: creatinine, LDH: lactic dehydrogenase, BUN: urea nitrogen, WBC: White blood cells, N: neutrophils, HB: hemoglobin, HTO: hematocrit, PLT: platelets. CRP: C-reactive protein, CL: chlorine, K: potassium, NA: sodium

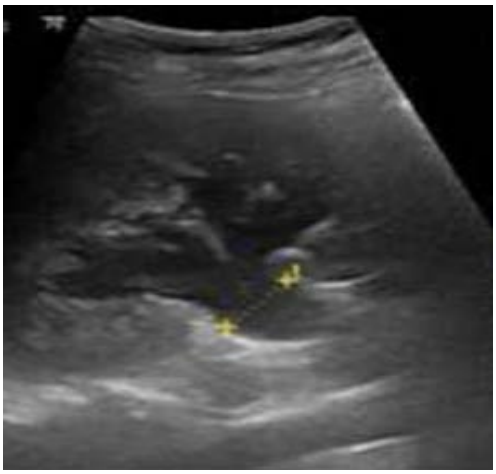

*Figure 1:* Renal and urinary tract ultrasound, coronal section. Grade II right hydronephrosis. Source: authors.

Based on platelet count findings, dengue with warning signs was considered as a differential diagnosis because it was located in an endemic area; but this diagnosis was later ruled out by both negative dengue IgG and IgM antibody tests. During her stay in the High Obstetric Risk Intensive Care Unit (seventh day of hospitalization and second day in the unit), she was assessed by the intensive medicine and critical care service, who, taking into account the intermittent fever, hypotension and systemic inflammatory response (tachycardia, tachypnea) despite management with broad-spectrum antibiotics (4 days of ampicillin/ sulbactam and two days of piperacillin/tazobactam at the doses described) and optimal fluid therapy, they consider a patient with septic shock and decide to start adjuvant therapy in the context of urinary focus shock with immunoglobulin G enriched with IgM and IgA at a dose of (5ml/kg/day) for 3 days. The patient's clinical evolution was monitored and she had persistent tachycardia (102 bpm) without tachypnea and without new febrile episodes. She was assessed by the infectious disease service (eighth day of hospitalization and third day in the unit) who considered continuing antibiotic escalation to ertapenem 1gr IV every 24 hours for 7 days due to persistent tachycardia and continuing with the last dose of immunoglobulin G enriched with IgM and IgA. The patient continued with satisfactory evolution, with blood pressure figures at goals, without requiring vasopressor support, with a progressive increase in platelet levels and improvement in the blood cell count (Table 4).

*Table 4:* Paraclinical

| |
|---|
| WBC: 12.000 |
| N: 76% |
| HB: 11 – HTO: 34 |
| PLT: 180.000 |

On day 4 of intravenous antibiotic therapy with ertapenem (twelfth day of hospitalization, seventh day in the unit) the patient suddenly became tachypneic with saturations of 88%, for which a chest tomography was indicated (figure 2 and figure 3) where It showed a large left pleural effusion, which is why a thoracentesis was indicated, draining 620 cc of clear liquid without infectious characteristics in the bacterial culture cytology reading and a negative fungal test. Patient with immediate improvement after drainage of the pleural effusion; for which she was transferred to a general gynecological hospitalization receiving antibiotic treatment with stable vital signs, afebrile, without loss of fetal well-being evaluated by obstetric ultrasound, who completed antibiotic treatment and proposed adjuvant immunotherapy scheme with immunoglobulin G enriched with IgM and IgA with adequate drug tolerance and favorable clinical course.

No adverse events were recorded during the hospitalization of the mother and the administration of immunoglobulin G enriched with IgM and IgA, nor were subsequent maternal and perinatal complications documented during the course of pregnancy.

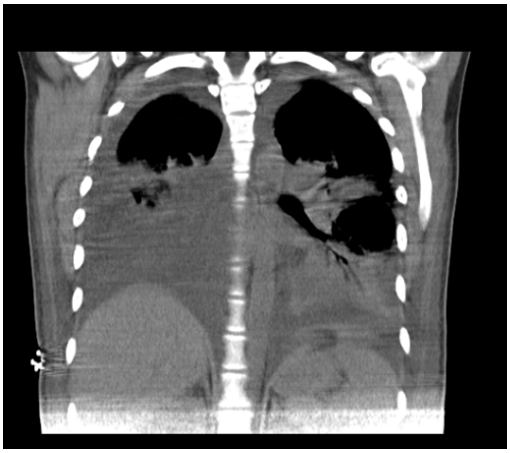

*Figure 2:* Chest tomography, coronal section. Bilateral pleural effusion. Source: authors.

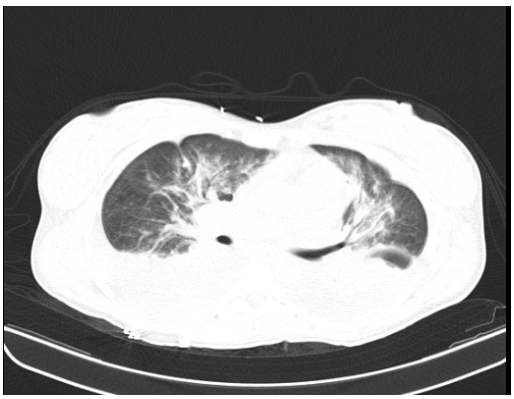

*Figure 3:* Chest tomography, axial slice. Bilateral pleural effusion. Source: authors.

## III. Discussion

Maternal sepsis corresponds to an obstetric emergency, and a leading cause of maternal and perinatal morbidity and mortality[14]. Timely and targeted antibiotic treatment and intravenous fluid resuscitation are essential for the survival of patients with suspected maternal sepsis. If the patient presents with septic shock or does not respond to initial treatment, multidisciplinary management and therapeutic alternatives are necessary. Among these alternatives are immunoglobulins.

Specifying the management and treatment of this pathology, it is considered that it is generally similar in both the pregnant and non-pregnant population. The international guidelines for the management of sepsis and septic shock 2021 proposed by the campaign surviving sepsis[15] establish some key points about what should be done when the diagnosis of sepsis is certain; these points are specified in table 5:

*Table 5:* Key points when sepsis is diagnosed

| KEY POINTS |
|---|
| 1. Measure the lactate level. |
| 2. Obtain blood and urine cultures before starting antibiotic therapy. |
| 3. Administer broad-spectrum antibiotics. |
| 4. Administer 30 cc/kg of crystalloids to avoid hypotension. |

The guide for sepsis care in pregnancy of the Royal College of the United Kingdom, and the Australian guide for sepsis in pregnancy consider that IgG enriched with IgM and IgA can be indicated as an alternative therapy in septic shock secondary to staphylococci and streptococci, recommending its use. use, but little evidence of its usefulness in sepsis due to gram-negative microorganisms has been reported; however, more studies and literature are expected to support the use of immunoglobulins in the context of obstetric sepsis of any origin[16,17].

Since 2012, the use of enriched immunoglobulins has been endorsed in the context of pregnant patients with sepsis who do not respond to initial management with antibiotics and intravenous fluids. According to the Sánchez-Padrón Guidelines for the care of severe sepsis in obstetric patients[18], the currently recommended dose for the pregnant population is 5 ml/kg/day (250 mg/kg of body weight/day) for 3 consecutive days with an infusion rate of 0.4 ml/kg/h; Additional infusions may be required depending on the clinical course of each patient. However, it should be noted that this drug is not commonly prescribed, few institutions routinely use it for severe infections, and there are still no established guidelines for how and when to use it.

There are very few reports that support the use of this type of medication in pregnant patients. A case of a patient in Turkey with a 29-week pregnancy and sepsis secondary to resistant acinetobacter is described. After 7 days of starting antibiotic therapy, her condition worsened, so they decided to start enriched immunoglobulin G (20 mg/kg/hr initial dose and continue 10mg/kg/hr for 68hrs) with subsequent response to management with immunoglobulins without associated adverse effects[19]. In this case, even higher doses were used than those usually recommended in this type of population. Likewise, there is another case published in the United Kingdom[20] of a patient who had a preterm birth at 32 weeks of gestation, developed sepsis due to GBS (group B streptococcus) 12 hours postpartum and, in addition to antibiotic therapy, therapy with enriched immunoglobulin G (in said study no dose or duration is specified). Two days after the established treatment, it begins to stabilize, a fact that justifies that the earlier the medication is started, the better results in terms of clinical evolution are expected. In Colombia to date, there is only one reported case of a patient with a 36-week pregnancy, who presented septic shock secondary to a gastrointestinal infection and progressed to multisystem organ failure in whom adjuvant therapy with IgM-enriched immunoglobulin was started with a good outcome. response and no maternal-perinatal complications at a dose of 5ml/kg/day for 3 days[21]; As administered in this case report, the patient in question had an excellent response to the established treatment, reducing the systemic inflammatory response in the context of septic shock of urinary origin.

## IV. Conclusion

A case of a 20-year-old primipregnant woman, previously healthy, with pregnancy in the second trimester, who developed sepsis of urinary origin, was presented. Initially, it was treated as a urinary tract infection with antibiotic management, but the patient did not respond to said therapy. Subsequently, antibiotic treatment was staggered and enriched immunoglobulin G was used as adjuvant therapy. Despite the initial form of presentation, the patient responded favorably from the clinical and paraclinical point of view after receiving the aforementioned treatment without presenting adverse effects or maternal-perinatal complications and continues her prenatal check-ups without documented sequelae. Among the strengths of this study, the use of a drug that can be used in pregnant women as adjuvant therapy in the context of sepsis and that could improve the maternal and perinatal prognosis should be highlighted. However, more studies and investigations should be carried out to evaluate the presence of adverse effects with the use of this drug in the short and long term, both in mothers and in newborns.

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# Study of Fetomaternal Outcome in Cases of Pre-Eclampsia

By Dr. Amsaveni, Dr. Meena Mehta, Dr. Varsha Oraon & Dr. Amulya Swati

*Abstract-* *Introduction:* Hypertensive disorders are among the most common medical disorders during pregnancy and continue to be a serious challenge in obstetric practice.

*Aims:* This study investigated the various risk factors, fetal and maternal outcome in cases of preeclampsia.

*Study Design:* This was a cross sectional study conducted over a period from January 2019 and June 2020. This study enrolled 100 cases of non severe preeclampsia and 100 cases of severe preeclampsia.

*Methods and Materials:* Participants were selected by consecutive sampling and baseline data were collected by using a predesigned and pretested structured questionnaire.

*Data Analysis:* Data were entered and analysed by using SPSS version 20.

*Keywords:* *preeclampsia, hypertensive disorders, fetomaternal outcome.*

*GJMR-E Classification:* *DDC Code: 618.2 LCC Code: RG524*


*Strictly as per the compliance and regulations of:*

# Study of Fetomaternal Outcome in Cases of Pre-Eclampsia

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*Results:* It was observed that preeclampsia was more common in the age group of 21 to 30 years (68%), women living in rural area (71.5%), low socioeconomic class, unbooked antenatal history (70%). Maximum number of patients were Primigravida (52.5%). 79.5% were anemic. 50% patients had vaginal delivery, 50% had Caesarean section. 73.5% babies born were full term alive babies, preterm were 20.5% (41), 4% (8) IUD and 2% (4) stillbirth .Early neonatal death occurred in 4.5% babies (9), 26% (52) babies were low birth weight, 18.5% were Growth restricted, 5.5% babies had Neonatal jaundice and 18.5% babies were admitted in Neonatal Intensive Care Unit. The most common maternal complication was Post Partum Haemorrhage (7.5%), which was observed in 15 cases, the next common complication was Abruption, which occurred in 10 cases (5%). Maternal mortality occurred in 2 cases (1%).

*Conclusion:* This study concludes that fetal and maternal outcome were markedly affected by preeclampsia and also the grave complications were more common in severe preeclampsia cases than in non severe preeclampsia cases. So proper Antenatal care, early diagnosis of preeclampsia and timely intervention will decrease perinatal morbidity and mortality.

*Keywords: preeclampsia, hypertensive disorders, fetomaternal outcome.*

*Author α ρ: Junior resident, Department of obstetrics and gynaecology Rajendra Institute of medical sciences, Ranchi.*
*e-mail: amssdude@gmail.com*
*Author σ: Associate professor, Department of obstetrics and gynaecology, Rajendra Institute of medical sciences, Ranchi.*
*Author ω: Senior resident, Department of obstetrics and gynaecology, Rajendra Institute of medical sciences, Ranchi.*

## I. Introduction

Hypertensive disorders are among the most common medical disorders during pregnancy and continue to be a serious challenge in obstetric practice. About 10% of pregnancies are complicated by hypertensive diseases [1]. They are one of the deadly triad along with haemorrhage and infection [2].

These disorders comprise of spectrum of diseases that include pre-existing hypertension (i.e., Chronic Hypertension), gestational hypertension, preeclampsia, chronic hypertension with superimposed preeclampsia, eclampsia, and HELLP syndrome. Among these, preeclampsia syndrome either alone or superimposed on chronic hypertension, is the most dangerous.

WHO reported the incidence of preeclampsia to be in the range of 2–15% in India, and India has an average of 4.5% [3]. Eastern and north eastern states of India were reported to have highest incidence of preeclampsia [4].

Criteria for hypertension- During pregnancy, hypertension is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure≥ 90 mmHg. Severe hypertension is defined as systolic blood pressure ≥ 160 mmHg and / or diastolic blood pressure ≥ 110 mmHg.

Preeclampsia refers to the new onset of hypertension and proteinuria or the new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation or postpartum in a previously normotensive woman [5, 6, 7, 8].

The diagnosis of preeclampsia with severe features is made when the women with preeclampsia who have severe hypertension and/or specific signs or symptoms of significant end organ dysfunction. The specific criteria are following [9].

1. Severe BP elevation- Systolic BP ≥ 160 mmHg and Diastolic BP≥ 110 mmHg on two occasions at least 4 hours apart.
2. Symptom of CNS dysfunction-1.New onset cerebral or visual disturbances such as Photophobia, scotomata, cortical blindness and retinal vasospasm 2.severe headache.
3. Hepatic abnormality- Impaired liver functions characterised by serum transaminase concentration

more than two times the upper limit of normal range or severe persistent right upper quadrant or epigastric pain unresponsive to medications.
4. Thrombocytopenia < 100000 platelets/$\mu$L.
5. Renal abnormality- Serum creatinine > 1.1 mg/dL or a doubling of serum creatinine concentration in the absence of other renal disease.
6. Pulmonary edema.
7. Uteroplacental dysfunction- fetal growth restriction changes in doppler velocimetry studies of the umbilical artery especially if combined with uterine arteries.

The study was undertaken to study the management of preeclampsia, fetal and maternal outcome in preeclampsia and to correlate outcome to various responsible factors so as to include clinical knowledge of preeclampsia among the various group of patients and draw out a policy for management to improve maternal and fetal morbidity & mortality.

*a) Aims and Objectives of the Study*

1. To Study various risk factors responsible for increased fetomaternal morbidity and mortality.
2. To study the maternal outcome in terms of severity, complications of preeclampsia and maternal mortality.
3. To study the fetal outcome in terms of morbidity and perinatal mortality.

## II. Materials and Methods

*a) Study Design and study population*

This was a hospital based cross-sectional observational study, conducted between January 2019 and June 2020. 100 cases of non severe preeclampsia and 100 cases of severe preeclampsia admitted in Department of Obstetrics & Gynaecology in our institute. The study was approved by institutional ethical committee memo no 62, IEC RIMS, Ranchi.

*b) Inclusion Criteria*

1. All cases of severe preeclampsia.
2. All cases of non severe preeclampsia.
3. All cases of preeclampsia with complications related to preeclampsia.

*c) Exclusion Criteria*

1. Patients with BP ≤140/90mmHg.
2. Patients who presented with convulsions.
3. Cases of Preeclampsia with medical complications which affect fetomaternal outcome. e.g.: Heart disease, Chronic hypertension, Diabetes, Haemoglobinopathies, connective tissue disorders, primary renal disorder.
4. Cases with obstetric complications not related to Preeclampsia e.g.: Placenta previa, Polyhydramnios.
5. Cases with Multifetal gestation.

*d) Ethical consideration*

The study was approved by the institutional ethics committee before commencing the study.

*e) Data collection procedure*

Data on socio-demographic variables and obstetric characteristics were collected by using predesigned and pretested structured questionnaire. After admission in the antenatal ward, the patients were monitored for blood pressure, any imminent symptoms, proteinuria, fetal heart rate tracings. Details of labour, spontaneous or induced, and mode of delivery were recorded. Maternal complications were noted. Newborn's birth weight and condition at birth were recorded. All newborns were followed up to 7 days of their birth to determine the perinatal outcome. At the end of the study, the data was compiled and analyzed.

*f) Data analysis*

Data were entered and analysed by using SPSS version 20. Significance of statistical association were tested at P-value <0.05.

## III. Results

*a) Socio Demographic Factors*

It was observed that preeclampsia was most common in the age group of 21 to 30 years, women living in rural area, low socioeconomic class and in women with unbooked antenatal history. There was significant association of preeclampsia with above socio-demographic variables (Table No: 1).

Maximum number of patients in the study were Primigravida (52.5%). 43.5% cases belonged to second, third and fourth gravida. 4% of cases in the study were grand multigravida (Gravida ≥5).

Among the 200 patients with pre-eclampsia 8 % patients presented in gestational age of 28 to ≤34 weeks, 13.5% were in the group of >34 to ≤37 weeks, 78.5% were in >37 weeks.

Maximum number of patients were in gestational age >37 weeks.

*b) Anemia*

Most of the preeclampsia patients had anemia. Presence of anemia was statistically significant with the severity of preeclampsia. (Table No:2) 159 patients (79.5%) were anemic according to WHO definition of anemia (<11 gm%).

*c) Antihypertensive drugs*

All the patients of severe pre-eclampsia (100%) needed Antihypertensive drugs and 50% of non severe pre-eclampsia needed Antihypertensive drugs.

*d) Inj. MgSO4*

Inj. MgSO4 was used in 79% of severe preeclampsia for eclampsia prophylaxis in those cases where BP couldn't be controlled with antihypertensive drugs. Out of 79 patients who received Inj.MgSO4, only

one patient developed convulsions and 21 patients didn't receive any eclampsia prophylaxis, of these 3 patients developed convulsions.

*e) Mode of delivery*

50% patients had vaginal delivery, 50% had Caesarean section (Table No: 3).

*f) Maternal outcome*

Out of 200 cases of preeclampsia 134 patients (67%) had uneventful maternal outcome and in 66 patients (33%) the maternal outcome was eventful.

Although there was no statistical association between maternal outcome and severity of preeclampsia, the grave complications were more common in severe preeclampsia cases than in non severe preeclampsia cases.

The most common complication in the cases of preeclampsia was Post Partum Haemorrhage, which was observed in 15 cases (7.5%), the next common complication was Abruption, which occurred in 10 cases (5%).

HELLP Syndrome occurred in 7 cases of severe preeclampsia, Eclampsia in 4 cases, Pulmonary edema in 3 cases, Renal failure in 3 cases, Sepsis in 6 patients, Cerebrovascular Accident in 1 case and 11 patients needed ICU care.(Table No:4). Maternal mortality occurred in 2 cases (1%).

*g) Fetal Outcome*

Of the 200 babies 73.5% (81 from non severe and 66 from severe pre-eclampsia) were full term alive babies, preterm were 20.5% (41 babies), 4% (8 babies) IUD and 2% (4 babies) stillbirth. Early neonatal death occurred in 4.5% babies (9), 26% (52) babies were low birth weight, 18.5% were Growth restricted, 5.5% babies had Neonatal jaundice and 18.5% babies were admitted in Neonatal Intensive Care Unit. (Table No: 5)

## IV. Discussion

In our study majority of patients (68%) belonged to the age group of 21 to 30 years. Similar result was obtained by Kari Annapurna et al [22], Singh et al [23], Neha Kumari et al [16] and Dr. J B Sharma et al [24]. This is because most of the patients in our country get pregnant at this age group only.

There was preponderance of primigravida in preeclampsia cases (52.5%) i.e., 56% in non severe cases and 52.5% in severe cases. This was comparable with the results observed by various authors by Rakesh Gadsa et al [24] (66.6%), Parveen M. Aabidha et al [18] (61.2%) and Kishwara et al [14] (63.3%). In most of the literature on preeclampsia, this has been reported that preeclampsia is common among the primigravida [10, 11].The maximum number of patients (78.5%) were in the gestational age≥37 weeks, which is almost similar to study by Dr Ashok Kumar Kumawat et al (72%) [23].

In our study anemia was present in 79.5% patients. In another study 55.9% were anaemic [41]. Awol Yamane Legesse et al [30] (2019) reported only 19.6% anemia. This is because the prevalence of anemia in Jharkhand is 78.45% among pregnant women [31] and anemia itself is a risk factor for developing preeclampsia.

In our study 73.5% patients had spontaneous labour, only 22% had induced labour which is similar to the study by Al Mulhim A.-A et al [12] (22.8%) and elective caesarean section was done in 4.5%.

In our study 50% (100 patients) delivered vaginally and 50% (100 patients) underwent Caesarean section. Similar to Aabidha et al [18] study in which 48.3% patients delivered by Caesarean section. Kari Annapurna et al [22] observed 57.6% Caesarean section. In another study 43% delivered by Caesarean section [26]. It is more when compared with other studies by Singh et al (21.4%) [19] and Rathore R, Butt NF et al [27] (15%).

It is also observed that there was no significant statistical association between the number of Caesarean sections and severity of preeclampsia. This is similar to the study by Juhi Patel et al [17]. The incidence of caesarean section was higher in our study because, in our institute most of the cases were referred complicated and previous caesarean section cases.

Prematurity was the most common complication associated with pre-eclampsia, which was seen in 20.5% cases. Similar results have also been observed by Aabidha et al [22] (23.65%). This is less when compared to the studies by Shaila Khan et al [13] (2013) and Muhammad Ashfaq et al. [21] (2018). In both studies prematurity was present in 52% cases. Prematurity as a complication of preeclampsia is either due to spontaneous preterm onset of labour or due to preterm induction of labour [14].

In the present study 16% babies had birth asphyxia. This is close to the study by Singh et al [23] (21.4). Aslam et al. [29] at Karachi (2014). Incidence of MSL and Fetal Distress were high in these cases.

In the present study 18.5% babies born to preeclampsia cases were growth restricted. This observation is similar to the study by Juhi Patel et al [17] (2015), in which 21% had IUGR babies. While Shaila Khan et al [13] and Vajira HW Dissanayake et al [32] observed 50% and 48% respectively.

The perinatal mortality was observed in 10.5% cases. similar result was also observed by Singh et al [23] (12.5%). Rakesh P.Gadsa et al [20] and Parveen M. Aabidha et al [18] observed perinatal mortality 17.4% and 15% cases respectively. However lower perinatal mortality was observed by Al Mulhim A.-A et al [12] (3.36%). This variability could be due to differences in availability of medical facilities. Main causes of fetal mortality were birth asphyxia, prematurity and IUGR.

*a) Maternal outcome*

The most common complication in the present study was post partum haemorrhage, which was observed in 7.5% cases. This is similar to the study by Dr Ashok Kumar Kumawat et al [23] (7%) and Aabidha et al [18] (10.75%). Preeclampsia patients lack normal pregnancy hypervolemia, are much less tolerant of even normal blood loss than are normotensive pregnant women [2].

The next most common complication in our study was Abruption, which was present in 5% cases. Almost similar incidences (5.6%) were noted by Baha M Sibai et al. [28] and Rathore R, Butt et al at Lahore [27] (4%). Hypertension in pregnancy is a most important risk factor for Abruption (10-50%) [10].

HELLP syndrome is a form of severe preeclampsia and is the most serious haematologic complications of preeclampsia [28]. In the present study 7% cases of severe preeclampsia developed HELLP Syndrome. It is comparable to the study by Vithal Kuchake et al [25] and Baba M Sibai et al [28] where HELLP syndrome developed in 8% and 8.6% patients respectively.

In our study, 2% cases developed convulsions. It is comparable to the study by Ashok Kumar kumawat et al (3%) [23] This is less when compared with studies by Juhi Patel et al [17] (36%), Rathore R, Butt et al [27] (26%), Vithal Kuchake et al [25] (10%) and Allilaj Minire et al [15] (3.25%). Less number of preeclampsia cases was attributed to the proper selection of cases for eclampsia prophylaxis and timely administration of $MgSO_4$.

## V. Conclusion

This study highlights various risk factors for preeclampsia. Unbooked, young primigravida in advanced period of gestation are at greater risk for preeclampsia related morbidity and mortality.

Preeclampsia tends to threaten maternal health and fetal viability adding to maternal and neonatal morbidity & mortality. There is a high frequency of preeclampsia in our setting and consequences of preeclampsia for neonatal morbidity and mortality are alarmingly high. Treating and improving socioeconomic status will improve maternal and neonatal outcome in preeclampsia. Antenatal care and educating women on significance of symptoms will markedly improve perinatal morbidity and mortality.

Prematurity, growth restriction and Low birth weight are neonatal complications to be anticipated and dealt with, when the mother has preeclampsia. A good Neonatal Intensive Care Unit (NICU) will help to improve neonatal outcome. Prompt treatment and management of its complications will certainly improve maternal and fetal complications.

Reversing the present trend in maternal health seeking behaviour is therefore an issue that needs to be effectively addressed if significant improvement in maternal health is to be achieved.

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*Table 1:* Socio-Demographic Factors in cases of Preeclampsia (N=200)

| S.No | Variables | Frequency | | | |
|---|---|---|---|---|---|
| 1. | Age in years | Non-severe preeclampsia | Severe preeclampsia | Total | P |
| | <20 | 24 | 20 | 44 (22%) | P=>0.05 |
| | 21-30 | 65 | 71 | 136 (68%) | |
| | >30 | 11 | 9 | 21 (10.5%) | |
| 2. | Residence | | | | P=>0.05 |
| | Rural | 67 | 76 | 143 (71.5%) | |
| | Urban | 33 | 24 | 57 (28.5%) | |
| 3. | Socioeconomic status | | | | P=>0.05 |
| | Upper | 0 | 0 | 0 | |
| | Upper middle | 3 | 2 | 5 (2.5%) | |
| | Lower middle | 14 | 8 | 22 (11) | |
| | Upper lower | 22 | 32 | 54 (27%) | |
| | Lower | 61 | 58 | 119 (59.5%) | |
| 4. | Booking History | | | | P=>0.05 |
| | Booked | 38 | 22 | 60 (30%) | |
| | Unbooked | 62 | 78 | 140 (70%) | |

| | | | | | |
|---|---|---|---|---|---|
| 5. | Gravidity | | | | P=>0.05 |
| | 1 | 56 | 49 | 105 (52.5%) | |
| | 2,3,4 | 41 | 46 | 87 (43.5%) | |
| | ≥5 | 3 | 5 | 8 (4%) | |

*Table 2:* Distribution of Anemia in Preeclampsia cases (N=200)

| S. No. | Anemia (Hb<11 gm%) | Non-Severe preeclampsia | Severe preeclampsia | Total |
|---|---|---|---|---|
| 1 | Not Anemic | 33 | 18 | 51(25.5%) |
| 2 | Anemic | 67 | 82 | 149(74.5%) |
| Chi square $X^2$=4.10 | | | | |
| P value=0.038 P= <0.05 | | | | |

*Table 3:* Observation of Mode of Delivery in Pre-Eclampsia Cases (N=200)

| S. No. | Mode of delivery | Non Severe preeclampsia | Severe preeclampsia | Total |
|---|---|---|---|---|
| 1 | Vaginal delivery | 54 | 46 | 100(50%) |
| 2 | Caesarean section | 46 | 54 | 100(50%) |
| Chi square $X^2$=1.28 | | | | |
| P value=0.254 P= >0.05 | | | | |

*Table 4:* Observation of Maternal Complications in Preeclampsia cases (N=200)

| S No | Maternal complications | Non Severe Preeclampsia (N/%) | Severe Preeclampsia (N/%) | Total |
|---|---|---|---|---|
| 1 | PPH | 12 | 3 | 15 (7.5%) |
| 2 | Abruption | 2 | 8 | 10 (5%) |
| 3 | HELLP syndrome | 0 | 7 | 7 (3.5%) |
| 4 | Sepsis/Infection | 3 | 3 | 6 (3%) |
| 5 | Pulmonary edema | 0 | 3 | 3(1.5%) |
| 6 | Acute Renal Failure | 0 | 3 | 3 (1.5%) |
| 7 | Eclampsia | 0 | 4 | 4 (2%) |
| 8 | CVA | 0 | 1 | 1(0.5%) |
| 9 | ICU Admission | 0 | 11 | 11(5.5%) |
| 10 | Death | 0 | 2 | 2(0.5%) |

*CVA- Cerebro Vascular Accident; ICU-Intensive Care Unit; PPH- Post Partum Haemorrhage*

*Table 5:* Observation of Fetal Outcome in Preeclampsia cases (N=200)

| S No | Fetal Outcome | Non Severe Preeclampsia (N/%) | Severe Preeclampsia (N/%) | Total |
|---|---|---|---|---|
| 1 | Full term alive baby | 66 | 81 | 147 (73.5%) |
| 2 | Preterm alive baby | 26 | 15 | 41(20.5%) |
| 3 | Intrauterine death | 5 | 3 | 8(4%) |
| 4 | Stillbirth | 3 | 1 | 4(2%) |
| 5 | Birth Asphyxia | 15 | 17 | 32(16%) |
| 6 | Early neonatal death | 7 | 2 | 9(4.5%) |
| 7 | Low birth weight babies | 33 | 19 | 52(26%) |
| 8 | Newborn jaundice | 7 | 4 | 11(5.5%) |
| 9 | IUGR | 22 | 15 | 37(18.5%) |
| 10 | NICU Admission | 23 | 14 | 37(18.5%) |

*IUGR- Intra Uterine Growth Restriction; NICU- Newborn Intensive Care Unit*

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# Fractional CO2 Laser in the Treatment of Post-Menopausal Vaginal Atrophy

By Honório Sampaio Menezes, Elaine Sangalli Mallmann, João Evangelista Sampaio Menezes, Rodrigo Cadore Mafaldo, Roberto Chacur, Danuza Dias Alves, Nivea Maria Bordin da Silva Chacur, Vicenzo Stein de Vargas, Leandro Dias Gomes, Gisele dos Santos Barreto & Gabriella Andressa Marchesin de Castro

*Abstract-* *Introduction:* Similarly to other parts of the body, the vagina changes over time, and vaginal atrophy is a common condition in women between 45 and 55 years of age. It causes discomfort and psychological suffering, in addition to being the main cause of pain during sexual intercourse.

*Objective:* This study aimed to evaluate the use of intravaginal fractional CO2 laser in the treatment of atrophy of the vaginal mucosa, as well as its effect on symptoms such as itching, irritation, pain, dyspareunia, urinary incontinence, dryness, and loss of mucosal elasticity.

*Methods:* This is a prospective cohort of 14 menopausal women with vulvovaginal symptoms who were evaluated pre- and post-procedure with CO2 laser treatment using the Monalisa Touch® technique. Cytological examination and validated questionnaires were used in the assessment.

*Keywords:* *vaginal atrophy, vaginal rejuvenation, fractional CO2 laser.*

*GJMR-E Classification:* *DDC Code: 600 LCC Code: T47*


*Strictly as per the compliance and regulations of:*

# Fractional CO2 Laser in the Treatment of Post-Menopausal Vaginal Atrophy

## Fractional CO2 Laser in Post-Menopausal Women

Honório Sampaio Menezes [α], Elaine Sangalli Mallmann [σ], João Evangelista Sampaio Menezes [ρ], Rodrigo Cadore Mafaldo [ω], Roberto Chacur [¥], Danuza Dias Alves [§], Nivea Maria Bordin da Silva Chacur [χ], Vicenzo Stein de Vargas [ν], Leandro Dias Gomes [Θ], Gisele dos Santos Barreto [ζ] & Gabriella Andressa Marchesin de Castro [£]

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*Methods:* This is a prospective cohort of 14 menopausal women with vulvovaginal symptoms who were evaluated pre- and post-procedure with CO2 laser treatment using the Monalisa Touch® technique. Cytological examination and validated questionnaires were used in the assessment.

*Results:* The mean (standard deviation) age of the patients was 58.1 (8.5), ranging from 46 to 78. The analysis of the Bachmann vaginal health index (VHI) showed a statistically significant difference ($p < 0.005$) between pre- and post-procedure, suggesting a substantial improvement in vaginal health. There was a significant increase in vaginal epithelial cells ($p<0.05$). No side effects were reported.

*Conclusion:* In addition to objectively demonstrating the improvement of vaginal cellularity, the results of the present study corroborate the physical, psychological, and social benefits of intravaginal CO2 laser technology for menopausal women in terms of quality of life.

*Keywords: vaginal atrophy, vaginal rejuvenation, fractional CO2 laser.*

## I. Introduction

Not long ago, the decline in sexual interest among women started before menopause, a period when estrogen production decreases gradually until the loss of libido and the appearance of uncomfortable symptoms in the perineal region. In a study published in 2014, Filippini stated that this painful and debilitating condition is often associated with psychological suffering and has a negative impact on women's lives. In addition to pain in the region, many women suffer from symptoms related to vaginal atrophy. These begin to appear between the ages of 45 and 55 and usually persist or even worsen over time. "This condition may cause dryness, irritation, burning, or pain during intercourse, affecting 40% of postmenopausal women"[1].

Salvatore, a pioneer in the application of *Monalisa Touch®* fractional CO2 laser, has published several studies assessing the effectiveness of this treatment in improving the symptoms of vaginal atrophy, and these have shown significant improvement in the physical and mental quality of life of the evaluated women[2].

According to Filippini[1] (2017), a clinical and histological study on the effectiveness of the Monalisa Touch® CO2 laser treatment in the restoration of the vaginal mucosa and lower urinary tract was presented at the 20th World Congress of the International Federation of Gynecology and Obstetrics (FIGO) held in Rome. Based on this study, the author has published several works confirming how promising the use of the Monalisa Touch®[3] has been.

In a study on a 12-week treatment with the Monalisa Touch® fractional CO2 laser, Salvatore et al. evaluated 50 women aged between 59.6 and 65.4 years who were dissatisfied with their previous local estrogen therapies. After three laser applications throughout the treatment, 42 women (84%) reported being satisfied with the procedure and experiencing minimal discomfort due to the insertion and movements of the probe during the first application. Data concerning the patients' physical and mental quality of life showed significant improvement[2].

After analyzing such positive data regarding the Monalisa Touch® treatment in women in Europe, the present study was designed to confirm those data and evaluate objectively (by histological examination) and subjectively the effects of the procedure on the vaginal mucosa.

*Author ¥: Avenida das Américas, 3301 – Bloco 4 – Sala 301 – Barra da Tijuca – Rio de Janeiro/RJ – Brasil.*
*e-mail: nucleodepesquisa@clinicaleger.com.br*

## II. Methodology

This is a prospective cohort study of 14 menopausal women with vulvovaginal symptoms (vaginal dryness, irritation, soreness, or dyspareunia). The patient enrollment required sexual activity at least once a month, no menstrual cycle for at least 12 months, and symptoms not alleviated by previous local estrogen therapy. Systemic or topical hormone replacement therapies within the past 6 months, acute or recurrent urinary tract infections, active genital infections, prolapse stage≥ II according to the pelvic organ prolapse quantification (ICS-POP-Q) system, and smoking constitute exclusion criteria.

*a) Study Protocol and Procedure*

The study was a prospective, outpatient setting. Prior to treatment, a complete gynecological exam was performed. The patients were recommended to avoid sexual activity for 3 days from each laser treatment session (mild inflammatory reaction may occur up to 48 hours).

In this study, a fractional microablative CO2 laser system (Rentall Medical Brazil, SmartXide2, *Monalisa Touch*®, DEKA Laser, Florence, Italy) was applied twice time using dot spacing1,000, dwell time 1,000, dot power 30 W, and 360° tip. Laser energy was transmitted through anintravaginal probe inserted into the vaginal canal (up to 12 cm).

*b) Data Collection*

Demographic data of the study population were gathered using a questionnaire applied before the first laser treatment.

Patients were evaluated before and after intravaginal CO2 laser treatment (Monalisa Touch®, SmartXide2, DEKA Laser, Florence, Italy). Two questionnaires were administered to assess vulvovaginal atrophy (VVA) symptoms using a visual analog scale (VAS) and the Bachmann vaginal health index (VHI). These were applied pre-treatment and 30 to 40 days after the second and third laser applications. The VAS scores were classified into three groups: mild (0-2), moderate (3-7), and severe (8-9).

Bachmann's VHI measures elasticity, secretion volume, vaginal pH, and epithelial integrity. The scale was used to assess vaginal itching, vaginal burning, pain during intercourse, vaginal dryness, and difficulty urinating or dysuria and categorize these symptoms into mild (0-2), moderate (3-7), and severe (8-9).

In order to observe vaginal cellularity, cytopathology samples were collected pre-treatment and 30 to 40 days after the last laser application.

*c) Data Analysis*

The collected data were reported as mean (standard deviation), median, and percentage (%). Analyzes were performed using the SPSS software version 25.0 (SPSS Science, Chicago, IL, USA). The paired-samples t-test and the signed-rank test were used to analyze continuous variables at a significance level of 0.05, corresponding to a 95% confidence interval.

## III. Results

The mean (standard deviation) age was 58.1 (8.5), ranging from 46 to 78 years.

The analysis of the Bachmann vaginal health index (VHI), which measures elasticity, secretion volume, vaginal pH, epithelial integrity, and lubrication, showed a statistically significant difference ($p < 0.005$) between pre- and post-procedure, suggesting a substantial improvement in vaginal health.

The data from the VAS regarding VVA symptoms showed overall improvement. When considering vaginal itching, nine patients (64.29%) reported that the condition improved, and five (35.71%), that it remained the same (without pruritus). The seven patients (50%) who had vaginal burning indicated improvement, while the rest of them did not have it. Pain during sexual intercourse improved for nine patients (64.28) but did not improve for one (7.14%); three (21.42%) remained abstinent and one (7.14%) did not feel pain. Regarding vaginal dryness, 11 patients (78.57%) reported improvement, two (14.28%) did not have this symptom, and one (7.14%) did not mention improvement. Difficulty urinating or dysuria affected seven (50%) patients; for six (42.86%) of them, it improved, and for one (7.14%), it remained the same. The mean time between applications was 116 days SD=66 (59-265).

There was a significant increase in vaginal epithelial cells ($p < 0.05$).

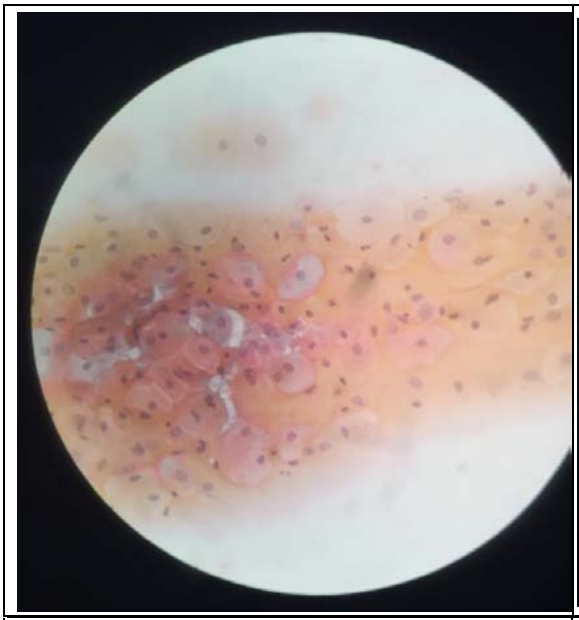

*Figure 1:* Atrophic smear – Patient A (pre-procedure).

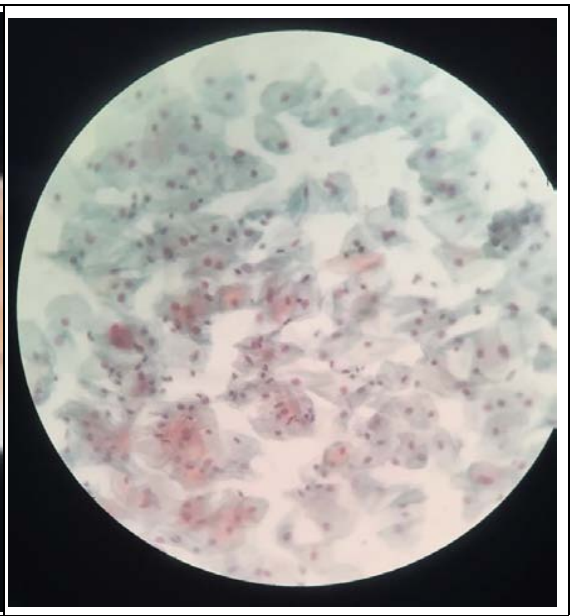

*Figure 2:* Normal smear– Patient A (post-procedure).

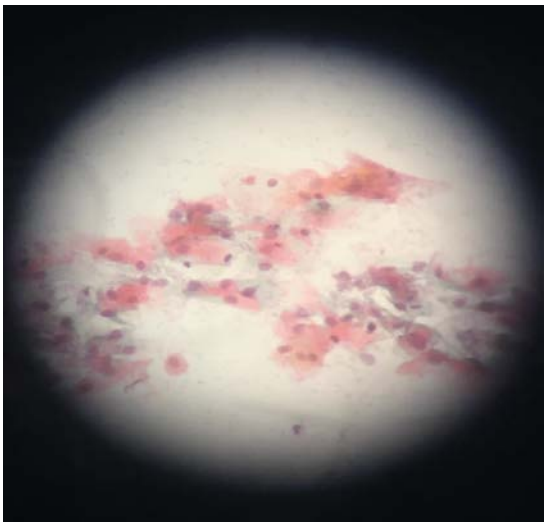

*Figure 3:* Atrophic smear– Patient B (pre-procedure).

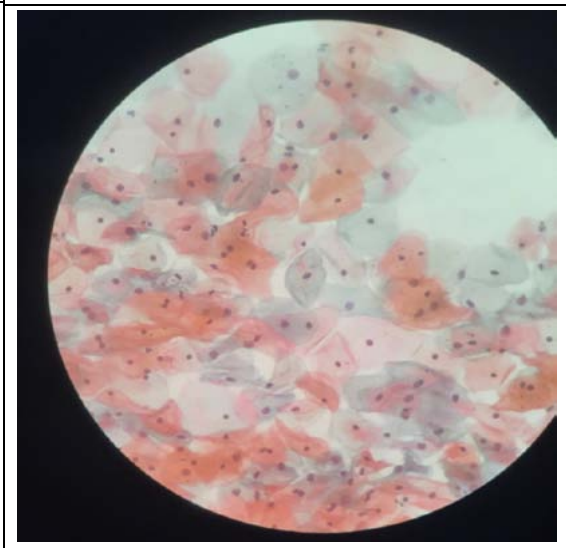

*Figure 4:* Normal smear – Patient B (post-procedure).

Figures 1 and 3 show pre-procedure images of vaginal epithelial cells with severe atrophy and low cellularity. Figures 2 and 4 show smears demonstrating post-procedure recovery of vaginal cellularity and normal epithelium.

## IV. Discussion

In recent years, there has been a greater demand for safe, effective, and long-term treatments of the deeper layers of the vaginal mucosa and the epithelium.

Non-invasive treatments for vulvovaginal atrophy VVA[4] symptoms are being researched, such as carboxytherapy and radiofrequency, in addition we also have fractional CO2 laser as a recent treatment option.

Relief of symptoms of vaginal atrophy can be achieved by non-surgical therapies, including fractional CO2 laser [5]. This type of laser produces rapid transient changes in cellular metabolism. The local production of collagen synthesis, induction, coordination and expression of growth factors are induced by the acute thermos-ablative damage produced by the laser [6].

As reported by Enemchukwu, the CO2 fractional laser application is an effective way for the relief of symptoms in vaginal atrophy, even one year after the procedure[5].

Significant improvement in VVA symptoms after three sessions of fractional CO2 laser and improvement in quality of life were reported by Perino et al. [6] 30 days after the last laser application. These finding could be corroborated by the present study, even after only two applications of fractional CO2 laser. Our study showed significant improvement in VVA symptoms after a month of follow-up fractional CO2 laser therapy.

VVA symptoms in 28 healthy post-menopausal women undergoing treatment with 3 sessions of intravaginal fractional CO2 laser was evaluated one, 3 and 6 months post-laser; in this study Eder et al (2018) [7] showed improvement in VVA symptoms and an increase in the Female Sexual Functioning Index (FSFI) from one month after the first treatment. This same finding had already been reported by Salvatore et al [8], in 2015, where the FSFI improved in the first 12 weeks after intravaginal CO2 laser application.

The VHI, studied by Arroyo (2017) showed improvement up to the eighth month after CO2 laser treatment [9].

According to Filippini & Farinelli, the Monalisa Touch® is an innovative CO2 laser treatment developed by DEKA which gently acts on the vaginal tissues to stimulate collagen production, improve the functionality of the treated area, and restore the propermucosal trophic balance. In another study, the author used the same method to treat postpartum dyspareunia. A significant improvement in symptoms could be observed in 5 to 6 patients, especially regarding dryness, dyspareunia, and pain in the vulval-perineal region. It is also noteworthy that most of these patients tried, without success, alternative therapies such as physical therapy, perineal massage, and tranquilizers[1].

Arroyo[9] performed a clinical and histopathological evaluation, as suggested by Salvatore et al [8], and found improvement in elasticity, secretion, epithelial integrity, lubrication and histopathological aspects, without reporting side effects.

Tahereh et al. (2020) compared intravaginal CO2 laser and the application of hormone therapy with Premarin vaginal cream. They demonstrated how the laser was betterat improving sexual desire, orgasms, and sexual satisfaction, and at decreasing pain during intercourse and overall sexual function in menopausal women. In the present study, no comparison was made with another treatment[10].

In a recent study, Macrene et al. (2021) demonstrated persistent positive effects in vulvovaginal treatment after one year of postmenopausal fractional CO2 laser treatment[11]. The limitation of their study was the use of a small sample; however, the statistical significance found indicates that it did not affect the results.

Our study has the particularity of evaluating the cellular changes of the vaginal mucosa, objectively proving its improvement and recovery after the application of fractional CO2 laser. Furthermore, a significant improvement in objective signs and symptoms of genital function could also be seen.

## V. Conclusion

In addition to objectively demonstrating the improvement of vaginal cellularity, the results of the present study corroborate the physical, psychological, and social benefits of the Monalisa Touch® fractional CO2 laser technology for menopausal women in terms of quality of life.

*Ethical Considerations*

This study was approved by the Research Ethics Committee of the Moinhos de Vento Hospital under protocol number 81915417.0.0000.5330.All participants signed a written informed consent form. The study was conducted according to the guidelines of the Declaration of Helsinki.

*Conflict of Interests*

The authors declare no conflict of interest.

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# Methods for Assessing Human Embryos to Increase Reproductive Potential

By Surayyo Yuldasheva

*Tashkent Pediatric Medican Institute*

*Abstract-* The embryological stage of ART programs is one of the most important, since the assessment of the quality of oocytes, their fertilization and in vitro cultivation to the stage of preimplantation embryos largely determines its success. Morphological evaluation of embryos is the main method of embryo selection. Time-lapse microscopy is one of the modern methods of selecting a high-quality embryo for transfer. In the analysis of many retrospective and prospective studies, they emphasize the advantage and lack of differences compared to traditional morphological assessment of the quality of embryos Almost all publications devoted to time-lapse microscopy have focused on determining the timing of specific events of embryo division and then using this information to create algorithms that help to select embryo for transfer.

*Keywords: assisted reproductive technologies, infertility, elective blastocyst transfer, time-lapse microscopy.*

*GJMR-E Classification: NLM: WQ 500*


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# Methods for Assessing Human Embryos to Increase Reproductive Potential

Surayyo Yuldasheva

*Abstract-* The embryological stage of ART programs is one of the most important, since the assessment of the quality of oocytes, their fertilization and in vitro cultivation to the stage of preimplantation embryos largely determines its success. Morphological evaluation of embryos is the main method of embryo selection. Time-lapse microscopy is one of the modern methods of selecting a high-quality embryo for transfer. In the analysis of many retrospective and prospective studies, they emphasize the advantage and lack of differences compared to traditional morphological assessment of the quality of embryos Almost all publications devoted to time-lapse microscopy have focused on determining the timing of specific events of embryo division and then using this information to create algorithms that help to select embryo for transfer.

*Keywords: assisted reproductive technologies, infertility, elective blastocyst transfer, time-lapse microscopy.*

## I. Introduction

The process of morphological study of embryos is one of the most important selection methods, the results of which evaluate a whole group of indicators, such as the number of blastomeres, the proportion of fragmentation, the severity of compaction, size and shape, as well as their correspondence to the stage of development, the formation of the blastocyst, the size of its cavity, the state of the internal cell mass with trophoblast [1, 2]. An efficient method of embryo selection is currently in high demand in this field, since it is a method of selecting embryos that have the highest potential for implantation [3]. The method of continuous video surveillance allows the specialist to obtain a long and detailed chronicle of the development process of each individual embryo. In the process of development, the embryo goes through several stages of development, and the duration of each stage also serves as a significant indicator of quality and potential, which is characterized as developmental kinetics [4]. In this regard, the introduction of time-lapse technology made it possible for embryologists to arm themselves with an effective tool for selecting promising embryos [5].

The aim of the study is to develop an algorithm for optimizing the in vitro fertilization program with a differentiated approach to the use of time-lapse technology or video surveillance of the development of embryos and artificial intelligence, which allow automatic formation of the morphodynamical profile of a human embryo based on video recording of the process of cultivating a human embryo to the blastocyst stage.

*Author: MD, PhD, Department of Obstetrics and Gynecology, Tashkent Pediatric Medican Institute, 223 Bogishamol str., Tashkent, Uzbekistan. e-mail: author.uzb@mail.ru*

## II. Materials & Methods

The study was carried out on the basis of CJSC Medical Company IDK (Samara, Russia) in the period from 2016 to 2019. Human embryos were used in the work, the study of which was carried out in compliance with international ethical and legal standards for the treatment of human embryos [Art. 18. Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being in the Use of Biology and Medicine, 1997]. Permission for the use of embryos in research was obtained from the Committee on Bioethics at the Samara State Medical University (excerpt from protocol No. 116 dated October 3, 2018) [6, 7]. Written consent was obtained from the patients included in the study to participate in the study. Exclusion criteria from the study included all conditions in which it is necessary to cancel the ET embryo transfer procedure in a cycle. Examination of patients in the ART program included a comprehensive examination, including the study of anamnesis, gynecological examination, laboratory tests and instrumental studies. ART was performed in accordance with the accepted standards of medical care in CJSC IDK Medical Company. Gametes and embryos were identified under the control of a stereomicroscope (Nicon, Japan). For incubation at 5% O2, COOK incubators (Australia) were used.

Transvaginal ovarian puncture was carried out at 36-37 hours after the start of the ovulation trigger. The identification of oocyte-cumulus complexes in the follicular fluid was carried out using a Nikon stereomicroscope (Japan), after which they were removed with a sterile micropipette. The complexes were washed and cleaned from liquid and blood using a HEPES buffer solution (G-mops, Vitrolife, Sweden). After counting the oocytes, they were transferred to special cups with a central well (Nunc) containing G-IVF+ culture medium (Vitrolife, Sweden) for pre-incubation for 2-3 hours (conditions: CO2 - 6%, O2 - 5%, at a temperature of 37°. After incubation, mechanical and enzymatic removal of cumulus cells (denudation of oocytes) was carried out. In this case, the complexes were placed in a hyaluronidase solution for 30 seconds, followed by washing from enzymes in a buffer solution

by a mechanical method. 5–6-day old blastocysts were examined according to a system based on classification (D.K. Gardneretal., 1999) and the RAHR Guidelines "Evaluation of oocytes and embryos" (Russia, 2021) [8, 9]. Over 100 cycles were analyzed using TimeLapse technology. The video surveillance system for embryo development included an incubator with an installed video camera Embryovizor (Russia). Embryos were cultured in special WOW dishes (Vitrolife, Sweden) in a universal medium Continius Single Culture (Irvine Scientific, USA) from 1 to 5-6 days of cultivation. There were no specific criteria for selecting patients for culture using this system [10]. The system has direct on-line access. To assess the development of embryos from days 1 to 5-6 of in vitro cultivation, the time of the first cleavages, the time range between the first and second cleavages, as well as the nature of cleavage (morphokinetics), and the time of blastocyst formation were taken into account. All of the above criteria served as predictors of the selection of embryos for transfer [11].

The criteria for elective transfer [12] of one embryo on the 5th day (5eSET) were: the presence of more than 2 embryos of excellent quality, the patient's age is up to 35 years, and the absence of previous IVF attempts in history. The criteria for selective single embryo transfer (5SET) were: the presence of a scar on the uterus after previous surgical interventions and other clinical situations.

Obtaining and processing information about human embryos was carried out in the laboratory of assisted reproductive technologies (ART) of the IDK Clinical Hospital of CJSC IDK Medical Company (Mother and Child group of companies, Samara, Russia). Graphic data and markup information have been uploaded to the SberCloud cluster. A convolutional network of neurons designed to differentiate embryos based on multiclass division [13] was installed on the Christofari supercomputer of the SberCloud cluster. To standardize the description of the development of human embryos cultured in vitro, we introduced the concept of "Morphodynamic profile of a human embryo" [14]. It includes a set of morphokinetic states identified by us, located on the time scale in accordance with the moment of their registration. All time cutoffs (points) are given in chronological order relative to the moment of fertilization.

## III. Results & Discussion

The cultivation of human embryos in vitro in the practice of embryological laboratories is currently a proven and standardized technique. The quality of media, consumables, technical capabilities of incubators make it possible to bring the conditions of growth and development of embryos in vitro as close as possible to natural conditions. Nevertheless, the problem of determining reliable predictors of the developing embryo, which has the highest chances of implantation, is extremely relevant. These aspects are especially significant in order to safely and effectively implement the strategy of transferring a single embryo into the uterine cavity to prevent the development of multiple pregnancies, the birth of premature and low birth weight babies. In this regard, the development of non-invasive technologies for ranking developing embryos in order to select them for transfer to the uterine cavity in a modern embryological laboratory is extremely in demand. A special term was also introduced – “morphokinetics”, which reflects the visual fixed state of the human embryo. Successive stages of the morphokinetic state constitute morphodynamics.

Monitoring the process of embryo development makes it possible to fix various stages of morphokinetic transformations, to establish the presence of cytoplasmic and extracytoplasmic structures - multinucleation, fragmentation, vacuolization, etc., and also to evaluate their contribution to the early development of embryos [15, 16]. At present, it is extremely important to identify the predictors of the development of a competent embryo, which determine its implantation potential [17]. Predictors in this case are prognostic parameters, the evaluation of which together serves as a method for differentiation and selection of embryos. For non-invasive monitoring of the pre-implantation development of human embryos, a multi-gas incubator with a reduced oxygen concentration (5%) with a video surveillance system Embryovizor (Westtrade, Russia) was used [18]. This equipment allows, without taking out a dish with developing embryos, to evaluate the first cell divisions, to determine the time intervals of embryo crushing, compaction and formation of blastocysts, and also detects intracellular changes [19].

During the analysis of video files, we can state signs of normal - 2PN2PB or abnormal fertilization (3PN) (Fig. 1, 2).

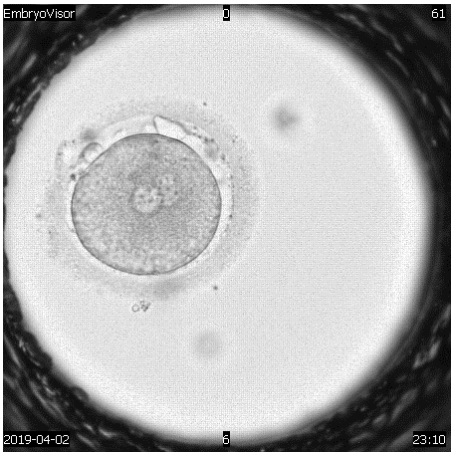


*Figure 1:* Human embryo of the 1st day of development at the 2PN2PB stage (zygote), magnification 200X.

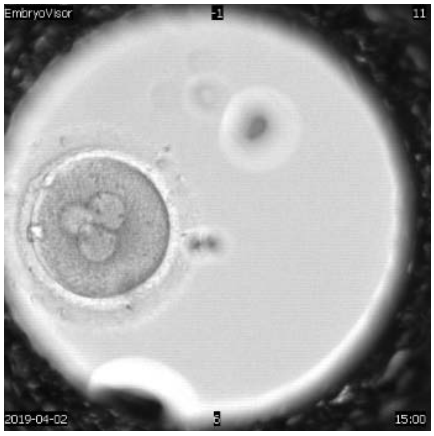


*Figure 2:* Human embryo of the 1st day of development at the 3PN2PB stage, magnification 200X.

The second feature is reverse crushing. If it is detected in the development of the embryo, this reduces its chances of implantation in the presence of others in which we have not recorded this feature (Fig. 3). The presented series of images show a series of frames that show the dynamics of the development of this process. In the first case, the embryo, which began division from the three-cell stage, goes through the stage of reverse cleavage into the two-cell stage.

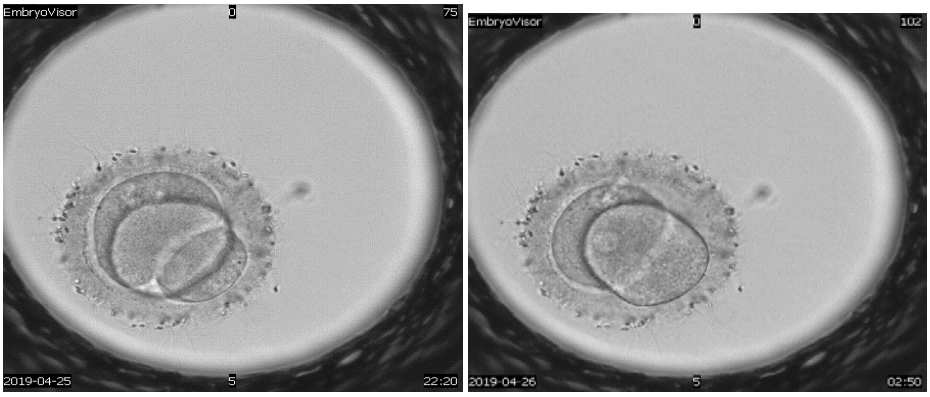


*Figure 3:* Reverse crushing of human embryos 3-2, magnification 200X.

In the second case, a normally divided embryo passes into a four-cell stage and returns to a two-cell stage (Fig. 4).

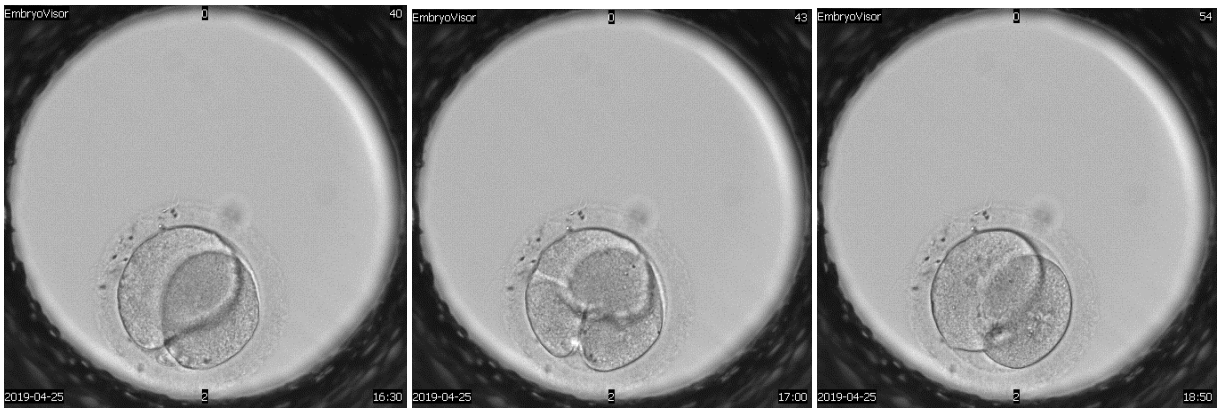


*Figure 4:* Reverse cleavage of 2-4-2 embryos, magnification 200X.

The appearance of multinucleation (several nuclei in developing blastomeres) is also a reason to exclude embryos for transfer and cryopreservation if other embryos of comparable quality are available.

That is, if there are embryos of a comparable organization, those that have reverse cleavage, multinucleation, play the role of a “reserve player” and

are subject to cryopreservation and transfer to the uterine cavity, if there are no other embryos.

Fragmentation - the appearance of nuclear-free fragments - is a variable and relative sign. Distinguish between small cell and cryocellular fragmentation. In accordance with our proposed classification for assessing the quality of developing embryos, the presence of fragmentation up to 10% is not a factor that reduces the competence of developing embryos. However, in the presence of a higher level of fragmentation, it can lead to its complete fragmentation or stop in development.

To standardize the description of the development of human embryos cultured in vitro, together with the developers of the Embryovizor system, the concept of "Morphodynamic profile of a human embryo" was introduced. It includes a set of morphokinetic states identified by us, located on the time scale in accordance with the moment of their registration. All time cutoffs (points) are given in chronological order relative to the moment of fertilization.

*Table 2:* Comparative characteristics of the indicators of the development of embryos obtained in the IVF program

| | IVF with Video n=32 | IVF without Video n=48 | IVF total n=80 |
|---|---|---|---|
| Average age of patients | 32,6±2,8 | 33,4±3,4 | 33,1±3,2 |
| Average attempts | 1,72±0,46 | 2,23±0,47*** | 2,03±0,53 |
| Average years of infertility | 5,56±1,01 | 5,63±1,16 | 5,6±1,1 |
| Average dose of FGS | 1457,1±269,7 | 1573,8±328,4 | 1527,1±309,8 |
| Medium MII | 6,5±1,48 | 5,69±1,19** | 6,01±1,36 |
| % fertilization | 74,1±13,9 | 76,7±14,3 | 75,6±14,1 |
| % crushing | 95,7±2,9 | 97,3±3,2** | 96,7±3,2 |
| % growth of doblastocyst | 18,4±4,2 | 22,3±5,7*** | 20,7±5,4 |
| Freeze % | 35±6,9 | 32,1±5,8* | 33,3±6,4 |
| average embryonic tolerance | 1,03±0,18 | 1,15±0,36* | 1,1±0,3 |
| HCG (+),% | 36,7±6 | 42,5±7,4*** | 40,2±7,5 |
| Ultrasound, % | 34,3±7,1 | 36±6,7 | 35,4±6,9 |
| CI, % | 36,9±8,9 | 39,3±7,3 | 38,3±8 |
| Multiple pregnancy rate | 8,22±1,72 | 4,77±0,86*** | 6,15±2,12 |

*Note: *-p<0.05, **-p<0.01, ***-p<0.001 statistical significance in relation to IVF group with video.*

The tables below show the main data on embryo development indicators and their analysis in a comparative aspect in groups with and without video monitoring.

When comparing the data in this group, we see that the indicators do not have a significant difference. However, it should be noted that the hCG and ultrasound values in the IVF group (with video) have a minimal difference, which indicates the high quality of the embryos that are cultured and selected for transfer using video surveillance technology. The multiple pregnancy rate, which is almost 2 times higher, confirms this conclusion.

When comparing the data in this group, we see that the indicators do not have a significant difference. It should be noted that the difference between hCG and ultrasound in the ICSI group (with video) is smaller, which indicates the high quality of the embryos that are cultured and selected for transfer using video surveillance technology. the lack of difference between CNB and CI indicates that all the embryos that gave birth were implanted. Moreover, the average number of embryos per transfer in this group is slightly lower than in the ICSI group (no video). The multiple pregnancy rate in the ICSI group (no video) is extremely high. This is a risk group, since obstetric risks and the risks of giving birth to premature and low birth weight children in this

group are extremely high. Attention should be paid to this group and a more rigorous selection of embryos for transfer should be carried out, while at the same time reducing the number of transferred embryos.

When comparing the older age group in this group, we see that the rates of growth to the blastocyst in the IVF group with video have higher values. this suggests that the continuous video surveillance and culture system has a positive and no negative effect on oocytes in older patients, whose oocytes are most sensitive to environmental fluctuations (light, temperature changes, CO2 levels, pH). Clinical indicators: hCG +, CNB have a minimal difference, which indicates the high quality of the embryos that are cultured and selected for transfer using video surveillance technology. The multiple pregnancy rate, which is more than 2 times higher, confirms this conclusion. Cleavage, Freeze, HCG+, CNB, Chi indicators show the advantage of selecting 1 best embryo using video surveillance. Most likely, this is due to stable conditions and reduced stress during the cultivation of embryos (no fluctuations in temperature, pH). In the ICSI group, when taking one embryo (SET - single embryo transfer) and transferring one best embryo (eSET - elective single embryo transfer) on day 5, compared with the general sample, higher rates of freezing, hCG+, ultrasound and CI were found.

These data strongly demonstrate the advantage of culturing embryos in a system with video surveillance. The absence of negative influence of external factors during cultivation, analysis of morphokinetics and more objective selection of embryos for transfer contribute not only to the formation of the most competent embryos, but also allow to achieve higher clinical indicators of CNB and CI [20].

In the study group, where TML was used, an increased probability of pregnancy was established, regardless of the option of embryo transfer: 5eSET - 70±8.5% and 5SET - 38.2±4.9%. In the study group, where the traditional method of cultivation and selection of the embryo was used, the pregnancy rate was 45% higher in the sample in which the elective transfer was performed: 5eSET - 55.6±6.7% and 5SET - 36.9±6.1%.

## IV. Conclusion

According to numerous publications, knowledge of the characteristics of the morphokinetics of a developing embryo makes it possible in some cases to predict its future fate. For example, the presence of direct division of the zygote into three blastomeres is an unfavorable marker and indicates a high level of aneuploidy of such embryos, while reverse division indicates a possible violation of cytokinesis. A short interval between the second and third cleavage is a prognostically favorable sign in the development of the embryo and most often demonstrates a high level of growth to the blastocyst stage. The fixed features of the morphodynamic profile are factors in the ranking of embryos and their selection for transfer and cryopreservation.

Based on the data obtained, we can draw the following conclusions:

1. Cultivation in an incubator with video surveillance allows the formation of embryos with a higher competence for implantation. In the study groups using video surveillance, higher results of hCG (+) / CNB were obtained and the difference between these indicators is minimal, which indicates a high quality of embryos that are selected for transfer (IVF 36.7 ± 6% / 34.3 ± 7.1 % with video surveillance and 42.5±7.4%/36±6.7% without video surveillance ICSI 30.1±6.6%/24.1±5% with video surveillance and 35±6.6%/ 25.3±4.9% without video surveillance).
2. In the group of older reproductive age (36+ years), the time lapse technology demonstrates even higher significance. The difference between hCG(+)/CNB values 34.7±8.1%/30.5±4.6% is minimal in the group with video surveillance. Most likely, this fact is associated with the high sensitivity of the oocytes and embryos of these patients to adverse environmental factors and stress, the implementation of which is reduced during cultivation in an incubator with a video surveillance system.
3. The fact of the highest rates of hCG (+) / CNB / CI 70 ± 8.5% / 59.9 ± 5.7% / 50.1 ± 8.2% in the group of elective single embryo transfer on day 5 (5eSET) using video surveillance technology indicates the high competence of these embryos.
4. Video surveillance technology for the development of embryos can reduce the influence of the human factor and increase the objectivity of assessing the structure of embryos, improving their selection, reducing the rates of multiple pregnancy.

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# Methods for Optimizing the Effectiveness of Assisted Reproductive Technology Programs using Pre-Implantation Genetic Testing

By Surayyo Z. Yuldasheva

*Tashkent Pediatric Medican Institute*

*Abstract-* These guidelines describe a study whose purpose was to analyze the feasibility of performing genetic screening of embryos (Next Generation Sequencing - NGS) as part of infertility treatment cycles, to determine the relationship or its absence between the stage of development of the embryo and its survival, as well as an indicator of the successful development of pregnancy with the previous genetic screening. Based on the results of a comprehensive study, the effect of genetic screening, vitrification, oocyte competence and clinical indicators of patients on embryo survival was established.

*GJMR-E Classification: NLM: WP 570*

# Methods for Optimizing the Effectiveness of Assisted Reproductive Technology Programs using Pre-Implantation Genetic Testing

Surayyo Z. Yuldasheva

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## I. Introduction

In each IVF cycle, specialists have to determine the embryo with the best morphology, predicting successful implantation and further development. But the structure of the embryo is not the only indicator of quality; chromosomal abnormalities can be hidden behind it. One of the factors of implantation and early reproductive losses are chromosomal aneuploidies, which lead to a halt in the development of the embryo. Therefore, determining the genetic profile of the embryo is the key to a successful pregnancy outcome.

Preimplantation genetic testing for aneuploidy avoids errors in the selection of the most promising embryo and significantly increases the success of implantation. Despite the fact that assisted reproductive technologies are becoming more and more widespread, the effectiveness of the IVF program is within 40%. The birth of a healthy child in a couple with any type of infertility depends on an incredible number of factors, but one of the key factors is the genotype of the embryo, which determines the survival and development of the latter. The ability to determine the quality of embryos is the cornerstone in a personalized approach to patient management and predicting the success of an IVF cycle.

According to the latest statistics, the number of children born with the help of assisted reproductive technologies (ART) on the globe has reached 8-10 million [2,4,6]. At the same time, despite the impressive figures, still up to 70% of artificially initiated ART cycles do not end in a successful birth of children. In this regard, the continuous search for innovative invasive and non-invasive methods for selecting embryos with the highest potential continues. The new Next Generation Sequencing (NGS) technology is a direct genome analysis method that makes it possible to screen the entire set of chromosomes for quantitative and structural abnormalities, which makes it possible to exclude embryos with corresponding disorders before the transfer procedure. The results of recent scientific work have convincingly proved the effectiveness of preliminary genetic screening for aneuploidy in the selection process in individuals over 35 years of age [7-9]. This is due to the fact that in women older than 35 years, a higher level of quantitative and structural disorders in the chromosome set is determined, and therefore the probability of pregnancy in this group of patients is the lowest [8,10].

The aim of the study was to analyze the feasibility of performing genetic screening of embryos (Next Generation Sequencing - NGS) as part of infertility treatment cycles, to determine the relationship or its absence between the stage of development of the embryo and its survival, as well as an indicator of the successful development of pregnancy with previous genetic screening.

Based on the results of a comprehensive study, the effect of genetic screening, vitrification, oocyte competence and clinical indicators of patients on embryo survival was established.

## II. Materials and Methods of Research

Transvaginal ovarian puncture was carried out at 36-37 hours after the start of the ovulation trigger. The identification of oocyte-cumulus complexes in the follicular fluid was carried out using a Nikon stereomicroscope (Japan), after which they were removed with a sterile micropipette. The complexes were washed and cleaned from liquid and blood using a HEPES buffer solution (G-mops, Vitrolife, Sweden). After counting the oocytes, they were transferred to special cups with a central well (Nunc) containing G-IVF+ culture medium (Vitrolife, Sweden) for pre-incubation for 2-3 hours (conditions: CO2 - 6%, O2 - 5%, at a temperature of 37 C. After incubation, mechanical and

*Author: MD, PhD, Department of Obstetrics and Gynecology, Tashkent Pediatric Medican Institute, 223 Bogishamol str., Tashkent, Uzbekistan. e-mail: author.uzb@mail.ru*

enzymatic removal of cumulus cells (denudation of oocytes) was carried out.In this case, the complexes were placed in a hyaluronidase solution for 30 seconds, followed by washing from enzymes in a buffer solution by a mechanical method.

For the vitrification of embryos, nutrient media from Irvine Scientific (USA) were used, based on the manufacturer's recommendations. Cryogenic preservation of embryos was carried out by direct and indirect exposure of the object to liquid nitrogen using open and closed type carriers (CryoTop, manufacturer Kitozato, Japan, Irvine Scientific, Sweden). After that, a retrospective study of cryoprotocol cycles was carried out on the basis of CJSC Medical Company IDK.

4 subgroups of SET (single embryo transfer) patients were selected for work:

– group 1 (n=20): included patients with NGS test cycles who underwent transfer of euploid embryos using their own oocytes;
– group 2 (n=446): included patients without NGS who underwent transfer of euploid embryos using their own oocytes;
– group 3 (n=8): included patients without NGS who underwent embryo transfer using donor oocytes;
– group 4 (n=62): an additional group of patients without NGS who underwent embryo transfer using donor oocytes. This group was singled out due to the relatively smaller number of samples in group 3.

Patients of the 1st, 2nd and 3rd groups were homogeneous with average ages of 34.1; 34.3 and 34.6 years. In the 4th group - 42.3 years. Thus, a total of 536 cryocycles were studied.

To assess the structure of oocytes and embryos, a morphological method for assessing the quality of embryos was used using an inverted microscope OlympusIX-73 (Japan) and a Nikon SMZ-1000 stereomicroscope (Japan). Embryo vitrification was carried out in accordance with the manufacturer's freeze/thaw protocol (Irvine Scientific, USA). To assess the viability of the embryo, its morphological assessment was performed immediately after thawing (Fig. 1) and 2 hours after thawing (Fig. 2).

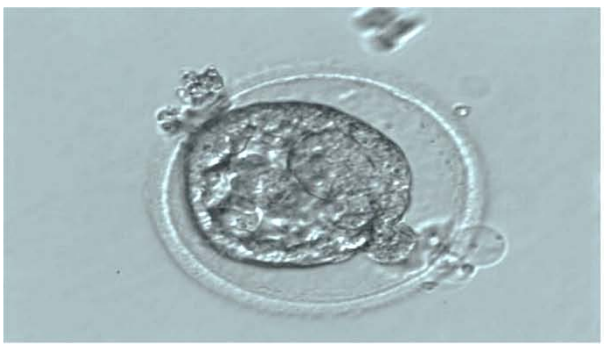


*Fig. 1:* Human embryo of the 5th day of development, the stage of the collapsed human blastocyst, immediately after defrosting. Boost: x200.

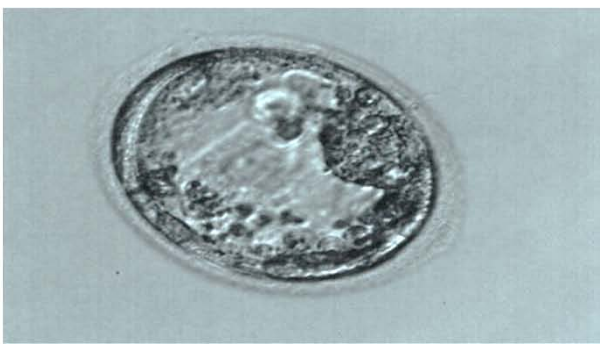


*Fig. 2:* Human embryo 5 days of development, human blastocyst stage 2 hours after thawing. Boost: x200.

Embryos were taken for transfer, in which the number of intact cells was more than 50%.

The embryo biopsy procedure was carried out within 5-6 days of the pre-implantation period. The selection of blastocytes of at least the 3rd category of SVV was carried out on the basis of the developed system for assessing the quality of embryos and the system proposed by D.K. Gardner and Schoolcraft 1999. The RAHR Guidelines (2021) for assessing the quality of developing human embryos in vitro were also taken into account.

The classification we proposed took into account a number of key indicators: the degree of ECM formation, the degree of TB formation, the absence or presence of fragmentation with an indication of its degree (0-10%, 10-25%, 25-50%, more than 50%), the absence or presence of vacuoles, the absence or presence of degeneratively altered cells.

Based on these indicators, the following were established:

1. The degree of expansion, that is, an increase in the size of blastocytes:

Based on the assessment of the above parameters in blastocysts, we determined:

i. The degree of expansion (increase in size) of the blastocyst:

1. early blastocyst, in which the cavity occupies less than half the volume of the embryo
2. blastocyst, in which the cavity occupies half or more of the volume of the embryo
3. complete blastocyst, the cavity is completely filled by the embryo, but the zona pellucida is not thinned
4. an enlarged blastocyst, the volume of the cavity is greater than the size of early embryos, and the zona pellucida is thinned
5. blastocyst, in which trophoblast cells began to emerge through the zona pellucida
6. blastocyst, completely out of the zona pellucid

ii. the degree of expression of the inner cell mass (ECM):

grade A - indicates densely packed ECM with many cells

grade B - ECM cells in large numbers, but weakly grouped class C - a small number of cells or their absence

iii. assessment of the severity of trophoblast (TB):

class A - TB consists of a large number of cells;

class B - TB is represented by a small number of cells or contains single flattened cells;

class C - TB has very few cells, they are very flattened or absent in some places.

Based on the results of a morphological study of embryos on days 5-6, they were ranked by quality (excellent; good; satisfactory; mediocre quality and stopped in development) (Table 1).

Preimplantation genetic screening included the following steps:

- stage of trophoblast biopsy;
- stage of biopsy washing (3-6 cells);
- the stage of cell fixation in a special buffer solution, followed by a molecular cytogenetic study.

Trophoblast biopsy was carried out on the 5th-6th day (at 120-144 hours after follicle aspiration) of in vitro embryo cultivation, provided that the blastocyst corresponds to art. development >3BB (according to D.K. Gardneretal). The procedure was performed using an RI micromanipulator (CooperSurgical, Denmark), a Laser Octa xMTG laser gun (Germany) for cutting the zona pellucida, and a COOK micropipette (Ireland) for cell biopsy and aspiration.

## III. Results and Discussion

One of the factors of implantation and early reproductive losses are chromosomal aneuploidies, which lead to a halt in the development of the embryo. Therefore, determining the genetic profile of the embryo is the key to a successful pregnancy outcome.

The procedure of preimplantation genetic testing for the presence of aneuploidy avoids errors in the selection of the most promising embryo and significantly increases the success of implantation. Despite the fact that assisted reproductive technologies are becoming more and more widespread, the effectiveness of the IVF program is within 40%. The birth of a healthy child in a couple with any type of infertility depends on an incredible number of factors, but one of the key factors is the genotype of the embryo, which determines the survival and development of the latter. The ability to determine the quality of embryos is the cornerstone in a personalized approach to patient management and predicting the success of an IVF cycle.

The proportion of chromosomal abnormalities in the structure of the causes of miscarriage is 50-80%, and the rate of aneuploidy in the case of positive morphological parameters is 44.9% (Rubio C., Bellver J. et all., 2017). The most modern and informative method to determine the quality of the embryo at the genetic level is the highly informative sequencing method - NGS. The material of the study was samples of the trophectoderm of embryos of 5-6 days of development obtained in IVF/ICSI cycles from 88 couples who were treated in the laboratory of assisted reproductive technologies of the IDK Clinical Hospital.

The age of women included in the study was up to 48 years. The distribution by age groups was as follows: patients under 35 years old accounted for 39% (34) of the total, women aged 35-37 years old were 20% (18), 38-40 years old - 17% (15), patients over 40 years old - 24% (21). All couples included in the study were divided into two groups - those with chromosomal abnormalities in one or both spouses, and couples with a normal karyotype of both spouses, for whom PGT was recommended for other reasons.

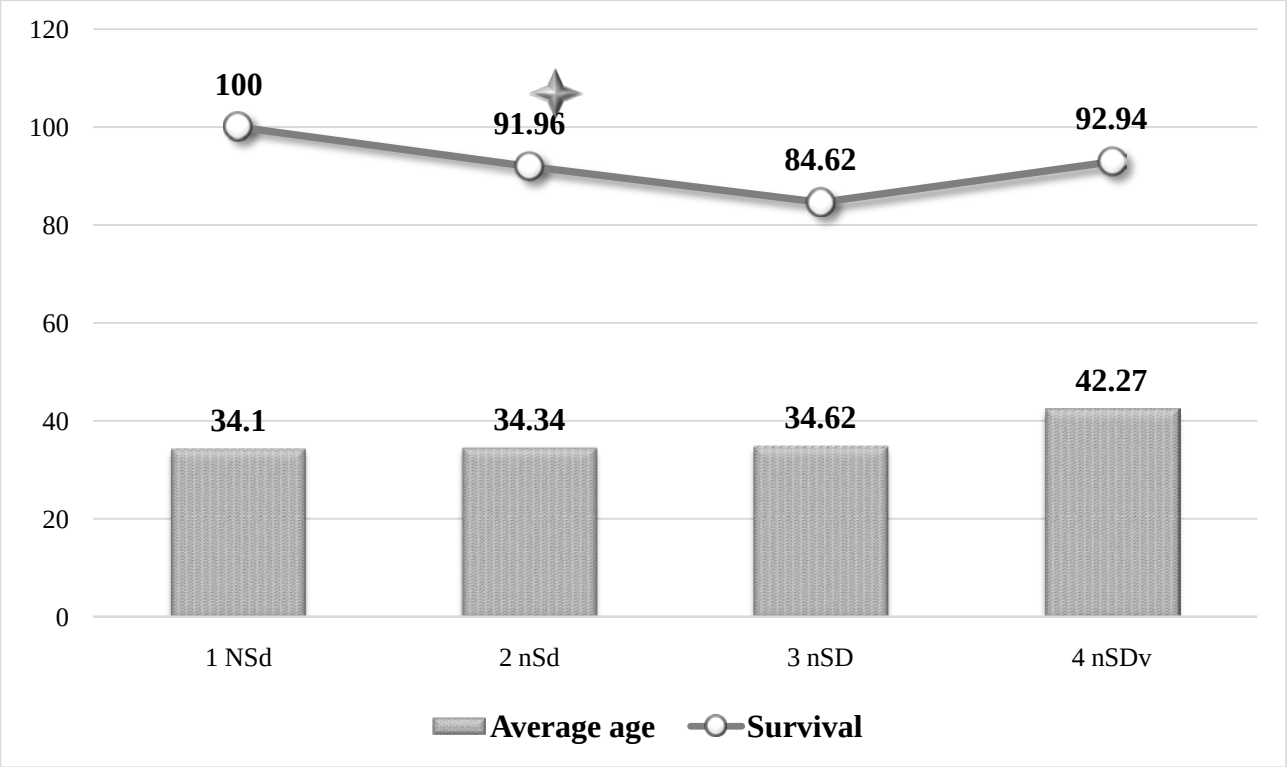
Women with a normal karyotype accounted for 89% (correspondingly, with chromosomal abnormalities - 11%), and men 93% (violations in the karyotype occurred in 7%). Couples without chromosomal disorders in any of the spouses were observed in 82% (72 pairs) in this sample, and with such - 18% (16 pairs). When analyzing differences in the studied indicator, the Mann-Whitney test (U) was used.

A total of 274 embryos were obtained using ART, which subsequently underwent PGT using the NGS method, the genetic material isolated from trophoblast cells obtained by blastocyst biopsy on days 5-6 after fertilization served as a sample. According to the results of PGT, 108 embryos (39%) were recommended for transfer, and 166 (59%) were not recommended. It should also be noted that in 5 cases (2%), the transfer was recommended only with the written consent of the patients, since mosaic embryos were observed. In pairs with a normal karyotype, the following results were observed - 43% (94) of embryos were recommended for transfer, and 56% (123) were not recommended. Among couples with a pathological karyotype in one of the spouses, 25% (14) of the embryos were euploid and recommended for transfer, and 75% (43) had some kind of anomaly. Using the Kruskal-Wallis test, it was shown that in patients with abnormalities in the karyotype, there are no statistically significant differences in the chance of getting an aneuploid embryo between different age groups. In patients with normal karyotypes, the probability of getting a euploid embryo decreased with age. In most cases, women with a healthy karyotype and an embryo recommended for transfer after NGS had a normal pregnancy (32%). It should also be noted that NGS revealed a large proportion of aneuploid embryos in the group of patients with abnormalities in

the karyotype, which is very important for making a decision on choosing an embryo for transplantation.

Based on the obtained results, it is fair to speak about the need for PGTA in couples with multiple failures in IVF cycles and chromosomal abnormalities in the karyotype of one of the spouses, since according to the results of NGS sequencing, it was found that most of the embryos in such couples cannot be recommended for transfer due to for chromosomal abnormalities (56% in healthy couples and 75% in couples with abnormalities in the karyotype of one of the spouses). In 5 cases, mosaic embryos were still recommended for transfer, but only with the written consent of the patient, which can be explained by multiple failures in IVF cycles and the hope that the genetic material of the trophectoderm and the inner cell mass is different. Among this sample of patients, we can predict a successful IVF cycle in 43% in healthy couples and 25% in couples with deviations in the karyotype of one of the spouses. In other cases, it is necessary to repeat the fertilization of the egg and subsequent PGTA. In 37.5% of cases, patients had a healthy pregnancy after transplantation of a euploid embryo. Speaking about the age of a woman, it should be noted that the probability of obtaining a euploid embryo is higher in younger women with a normal karyotype. In the case of a genetic abnormality in a woman's karyotype, age does not statistically affect the likelihood of obtaining a healthy embryo (Fig. 4). The blastocyte survival rate was studied to establish the degree of influence of the vitrification process on embryos that had undergone a previous biopsy with the separation of 3-5 trophoblast cells. It is worth noting that biopsies are invasive procedures and carry the risk of damage to the embryo in the process. The results of the study are shown in Figure 1.

The data presented in Figure 1 show that the survival rate of embryos in the study group 1 was 100%, which indicated that vitrification does not reduce the quality and viability of embryos after biopsy. It is possible that the high survival rate may also be associated with the previous selection of embryos with the highest potential. Statistical analysis revealed significant differences in survival rates between groups 1 and 3, as well as between groups 2 and 3, which indicates that survival in the group where donor material was used (group 3) was lower compared to groups 1 and 2, where own cells were used. At the same time, the age indicator did not affect survival in groups 3 and 4, where donor cells were used.




*(Note: * - statistical significance in relation to the 3nSD group).*

*Figure 1:* Embryo survival rates and clinical performance of ART programs

The lowest levels of hCG (+) were recorded in group 2, where own genetic material was used without previous genetic testing). Differences between groups 2 and 3, as well as 3 and 4 were statistically significant.

The study revealed the presence of comparable values in the analysis of CNB and NI in groups 1, 3 and 4, which indicated that genetic screening with the introduction of one's own oocytes makes it possible to obtain results close to the results when using donor

material without taking into account the age of the recipients. This fact is also evidence that the reproductive potential is determined by the properties of oocytes.

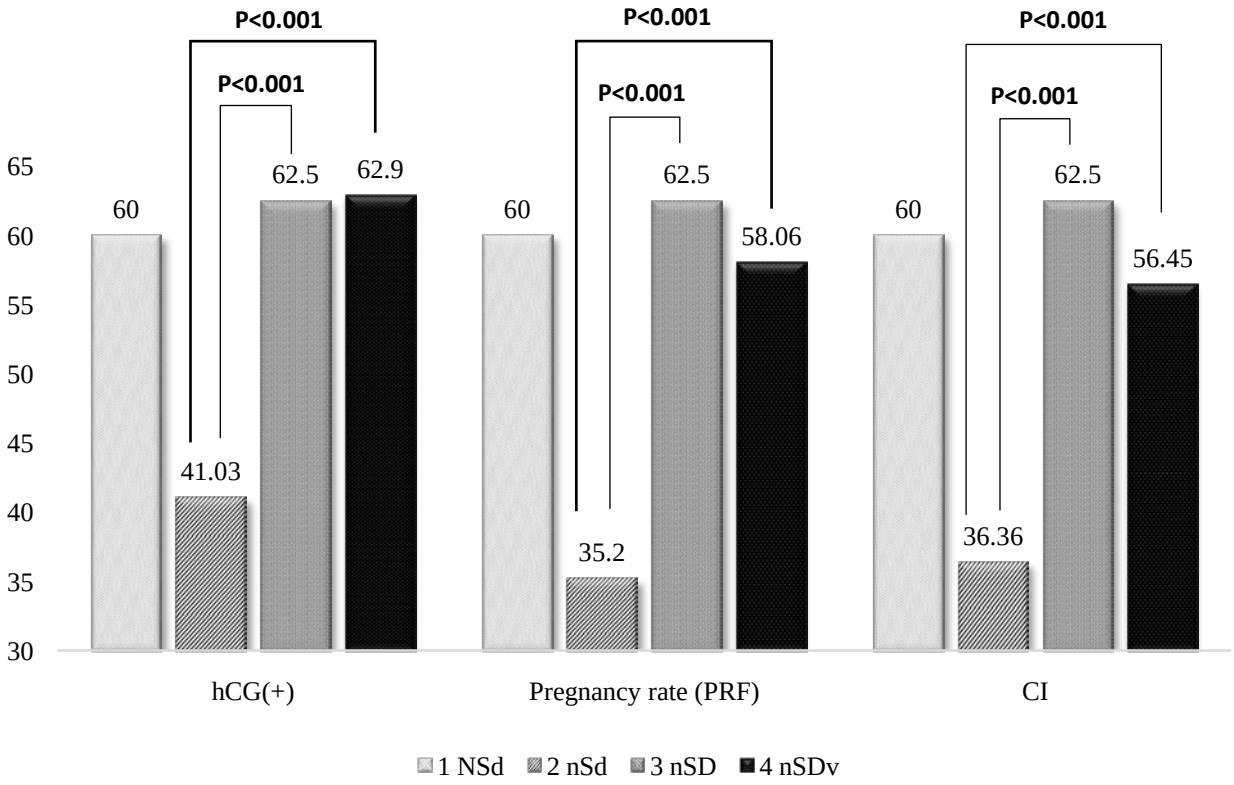



*Figure 2:* Results of a study of the clinical effectiveness of ART programs.

The graph shows that significant differences were established between groups 1 and 2, which confirms the effectiveness of the method of genetic screening and transport of a euploid embryo into the uterine cavity using its own material. Significant differences between the data of groups 2 and 3 also prove the effectiveness of using donor cells without previous genetic screening in the same age group. It also showed the advantage of using cryoprotocols (CNB, hCG frequency and CI) with transfer after NGS in the group using donor material.

## IV. Conclusion

Based on the results of a comprehensive study of the impact of genetic screening, vitrification, oocyte competence, and clinical indicators of patients on embryo survival, the following conclusions can be drawn:

- vitrification does not significantly affect the viability and quality of embryos, regardless of the biopsy;
- the main prognostic factor that affects the onset of pregnancy is the quality of oocytes and the degree of their ploidy;
- conducting genetic screening for the detection of aneuploidy significantly improves the results, bringing them closer to the results of patients who used donor material.

1. PGT is necessary in couples with multiple failures in IVF cycles and chromosomal abnormalities in the karyotype of one of the spouses, since according to the results of NGS sequencing, it was revealed that the majority of embryos in such couples cannot be recommended for transfer due to chromosomal abnormalities (56 % in healthy couples and 75% in couples with deviations in the karyotype of one of the spouses).
2. Among this sample of patients, we can talk about the high competence of embryos and their implantation ability in 43% in healthy couples and 25% in couples with deviations in the karyotype of one of the spouses. In other cases, repeated fertilization of the egg and subsequent PGT are necessary. In 37.5% of cases, patients of the two groups had a healthy pregnancy after transplantation of an euploid embryo (32% in the first group and 5.5% in the second).
3. Speaking about the age of a woman, it should be noted that the probability of obtaining a euploid embryo is higher in younger women with a normal karyotype. In the case of a genetic abnormality in a woman's karyotype, age does not statistically affect the likelihood of obtaining a healthy embryo.
4. Vitrification of 5–6-day old blastocytes makes it possible to carry out trophoblast biopsy and genetic

screening, which, in turn, increases the likelihood of pregnancy when using euploid material.

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- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

***Structure and Format of Manuscript***

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

## Format Structure

***It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.***

All manuscripts submitted to Global Journals should include:

**Title**

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

**Author details**

The full postal address of any related author(s) must be specified.

**Abstract**

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

**Keywords**

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

**Numerical Methods**

Numerical methods used should be transparent and, where appropriate, supported by references.

**Abbreviations**

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

**Formulas and equations**

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

**Tables, Figures, and Figure Legends**

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

**Figures**

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

## Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

## Tips for writing a good quality Medical Research Paper

***1. Choosing the topic:*** In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

***2. Think like evaluators:*** If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

***3. Ask your guides:*** If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

***4. Use of computer is recommended:*** As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

***5. Use the internet for help:*** An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

***6. Bookmarks are useful:*** When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

***7. Revise what you wrote:*** When you write anything, always read it, summarize it, and then finalize it.

***8. Make every effort:*** Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

***9. Produce good diagrams of your own:*** Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

***10. Use proper verb tense:*** Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

***11. Pick a good study spot:*** Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

***12. Know what you know:*** Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

***13. Use good grammar:*** Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

***14. Arrangement of information:*** Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

***15. Never start at the last minute:*** Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

***16. Multitasking in research is not good:*** Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

***17. Never copy others' work:*** Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

***18. Go to seminars:*** Attend seminars if the topic is relevant to your research area. Utilize all your resources.

***19. Refresh your mind after intervals:*** Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

***20. Think technically:*** Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

***21. Adding unnecessary information:*** Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

***22. Report concluded results:*** Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

***23. Upon conclusion:*** Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

## Informal Guidelines of Research Paper Writing

***Key points to remember:***

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

**Final points:**

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

*The introduction:* This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

**The discussion section:**

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

**General style:**

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

**To make a paper clear:** Adhere to recommended page limits.

*Mistakes to avoid:*

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

**Title page:**

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

**Abstract:** This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

*Reason for writing the article—theory, overall issue, purpose.*

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

**Approach:**

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

**Introduction:**

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

*The following approach can create a valuable beginning:*

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

**Approach:**

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

**Procedures (methods and materials):**

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

**Materials:**

*Materials may be reported in part of a section or else they may be recognized along with your measures.*

**Methods:**

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

**Approach:**

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

**What to keep away from:**

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

**Results:**

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

**Content:**

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

**What to stay away from:**

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

**Approach:**

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

**Figures and tables:**

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

**Discussion:**

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

**Approach:**

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

## The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

*Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection*.

*Segment draft and final research paper:* You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

*Written material:* You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

## Criterion for Grading a Research Paper (Compilation) by Global Journals

**Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.**

| Topics | Grades | | |
|---|---|---|---|
| | **A-B** | **C-D** | **E-F** |
| ***Abstract*** | Clear and concise with appropriate content, Correct format. 200 words or below | Unclear summary and no specific data, Incorrect form Above 200 words | No specific data with ambiguous information<br>Above 250 words |
| ***Introduction*** | Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited | Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter | Out of place depth and content, hazy format |
| ***Methods and Procedures*** | Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads | Difficult to comprehend with embarrassed text, too much explanation but completed | Incorrect and unorganized structure with hazy meaning |
| ***Result*** | Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake | Complete and embarrassed text, difficult to comprehend | Irregular format with wrong facts and figures |
| ***Discussion*** | Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited | Wordy, unclear conclusion, spurious | Conclusion is not cited, unorganized, difficult to comprehend |
| ***References*** | Complete and correct format, well organized | Beside the point, Incomplete | Wrong format and structuring |

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