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Self-Declared Infertility

Prevalence, Risks and Treatment

Highlights

Demographic and Health Survey

Oxytocin in Active Management

Discovering Thoughts, Inventing Future

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Self-Declared Infertility and Demand for Treatment. Findings from the National Demographic and Health Survey (PNDS) 2006

By Sandra Garcia & Joice Melo Vieira

University of Campinas

Abstract- *Objectives:* This article aims to identify and characterize women of reproductive age who declare themselves infertile or having difficulty conceiving and wish to have children, their demand for infertility treatments in public and private services, and their outcomes.

Methods: This study is based on the data on infertility available from PNDS 2006, a national household survey designed using complex probabilistic sampling with approximately 15.000 women of reproductive age representing the five Brazilian macro-regions. Chi-square tests were adjusted to identify associations between infertility, treatment-seeking, and sociodemographic variables. We calculate Cramer's V to measure the strength of the association between infertility and each sociodemographic variable of interest.

Keywords: *infertility, reproductive intention, search and access for infertility treatment, reproductive rights, brazil.*

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Sandra Garcia [α] & Joice Melo Vieira [σ]

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Results: Among women in non-reproductive conditions (7.1%), only 5.7% said they wanted to have children or more children. Almost half of them did not seek help. The characteristics more associated with not seeking help are low socioeconomic status, being resident in the North, Midwest, and Northeast regions, advanced age, and being black, in this order.

Conclusion: The study points to the need for the health system to improve access to fertility diagnoses and treatments in public health services, especially for the large population that depends on it to exercise their reproductive rights. It is also essential that health services promote information about the sharp decline in women's reproductive capacity after 30 years old.

Keywords: infertility, reproductive intention, search and access for infertility treatment, reproductive rights, brazil.

I. Introduction

Infertility is a severe public health problem that can affect both men and women and whose impact varies among different populations and acquires relevance for specific communities. It recognizes that infertility affects 10% to 15% of couples of reproductive ages worldwide. In 2009, the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) classified infertility as a disease of the reproductive system, establishing an international clinical and legal standard (Zegers-Hochschildet al., 2009)[(1)]. Its clinical definition *is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse*" (World Health Organization, 2011)[(2)]. Commonly neglected in developing countries, infertility brings couples social, economic, and psychological consequences.

The start of any treatment requires a diagnosis. Moreover, this is no different when it comes to infertility – the better the diagnosis, the better the treatment. The most cited causes of female infertility in the medical literature are tubal obstruction, pelvic inflammatory disease, chronic anovulation, endometriosis, sexually transmitted diseases (STD), and low ovarian reserve. For male infertility, the determinants are varicocele, exposure to specific chemical components, and the resulting qualitative and quantitative changes in semen. In general, recommendations for infertility treatment are drug therapies, correction surgeries, and medically assisted reproduction techniques.

The definition of infertility can vary according to the study area: clinical, epidemiological, or demographic, and it depends, according to each scientific field, on the length of exposure to the risk of pregnancy and whether couples seek live birth rather than conception (Mascaren has et al., 2012)[(3)]. This imprecision makes it challenging to compare the study's results. In Brazil, no clinical or demographic data points us to the magnitude of the problem, its social characteristics, and impact.

From a social perspective, this topic's need for data and public visibility is imperious. More and more women postpone the birth of their first child to gain professional qualifications and find economic stability. The national total fertility rate has remained below the minimum required for population replacement since 2003 (Rede Interagencial de Informações para a Saúde, 2014)[(4)]. That year, the fertility rate was 2.07 births per woman, and 2015-2020 is estimated at 1.7. The fertility of mature women has become increasingly relevant. In 2000, around 22,5% of the births were from mothers aged 30+ years old. In 2022, this percentage reached 38,5%. The accumulated number of births from mothers aged 50+ from 2000 to 2022 was 6324 cases, situations in which it is almost certain that some assisted reproduction technologies were used. The frequency of births in this age group is 3.6 times higher in 2022 compared to 2000.

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The National Demographic and Health Survey (PNDS) 2006 is part of the 5th Phase of the MEASURE DHS (Berquó et al., 2008)[5]. It is the most recent representative data on reproductive intentions, birth, and contraceptive use for Brazilian women of reproductive age. A new round of the PNDS took place in 2023, but the data was unavailable while this article was produced. However, the 2006 PNDS does not contain complete histories of stable union and the calendar of contraceptive use in the last five years before the survey; it is an instrument used to collect detailed information about the reproductive and contraceptive background. This is a necessary tool to calculate infertility from a demographic point of view. As we could not count on the complete calendar, we based our analysis on women's self-reports of infertility or difficulty conceiving. Anyway, the 2006 PNDS is an exceptional source because it was the first survey realized during the phase of total fertility rate below replacement level (2.1 births per woman) to consider a consistent set of valuable questions for infertility studies. As we will see in the discussion section, the National Health Survey (PNS) was carried out in 2013 and 2019. However, it raises some questions about infertility and does not address the topic as comprehensively as the 2006 PNDS. Even PNDS 2023 runs the risk of adopting a more superficial perspective on infertility.

This study aims to identify and characterize women of childbearing age who wish to become pregnant and declare themselves infertile or having difficulty getting pregnant. Therefore, the percentage of infertility calculated based on the women's statements should be understood as an approximate demand for infertility treatment, characterizing the likely users of these services. It also classifies women seeking treatment for pregnancy by type of service (private, health insurance, or SUS– Unified Health System, a public service) and their outcomes. It investigates the reasons why women did not seek help and associated factors.

II. Material and Methods

This study is based on PNDS 2006, a household survey of national representativeness of the five Brazilian macro-regions, urban and rural; 14,617 households were selected according to a stratified model of simple random conglomerates in two stages: lottery draw and household draw. Interviews were conducted with 15,575 women aged 15 to 49 in the selected households (Cavenaghi, 2008)[6]. The survey did not include interviews with male partners.

The PNDS 2006 data comes from complex probabilistic sampling; therefore, the statistical analyses considered the weights and the complex sample planning (Berquó et al., 2008)[5].

Based on this research, we classified women according to self-reported reproductive status: infertility/difficulty conceiving, menopausal, hysterectomized, sterilized, and whether they had an infertile partner. The survey topics dealing with fertility planning and reproductive intentions were selected, and questions about infertility and the desire to become pregnant were analyzed. Women who declared themselves pregnant, sterilized, or with vasectomized partners (28.9%) did not respond to the battery of questions about seeking infertility treatment.

The socio-demographic variables included are macro-region of residence, age group, socioeconomic status, and race. It should be clarified that socioeconomic status considers the educational level of the household's head, level of consumption, and access to goods and facilities. Additionally, there are five racial groups considered by the Brazilian statistical system: white, black, brown, indigenous, and Asian. Usually, the Black movements aggregate brown and black people in the same category because of their similar social disadvantages. In this paper, we work with a dichotomic variable: black (black and brown together) and, on the other side, not black (white, Asian, and indigenous). Pearson's chi-square tests were adjusted to identify associations between infertility, treatment-seeking, and those variables. The threshold of significance was set at p values <0.05. The Cramer's V was calculated to determine the magnitude of this association. The advantage of Cramer's V compared to other association measures is that it can be applied to any contingency table originating from two categorical variables, regardless of the number of rows and columns in that table. The Cramer's V value varies from 0 to 1, where 0 means no association and 1 means a perfect association. The association revealed by Cramer's V can be classified as negligible, small, medium, and large. The range of values that delimit each of these categories depends on the degrees of freedom (df)for the chi-square statistic: $df = (r - 1)(c - 1)$, with r the number of rows and c the number of columns of the contingency table.

Table 1: Cramer's V: magnitude of association for categorical tables according to degrees of freedom

Degrees of freedom	Negligible	Small	Medium	Large
1	< 0.10	< 0.30	< 0.50	≥ 0.50
2	< 0.07	< 0.21	< 0.35	≥ 0.35
3	< 0.06	< 0.17	< 0.29	≥ 0.29
4	< 0.05	< 0.15	< 0.25	≥ 0.25
5	< 0.05	< 0.13	< 0.22	≥ 0.22

Source: Cohen (1988)[7]

The analysis was performed using Stata v. nine and SPSS v.14 software.

III. Results

The large group who answered the questions (71.1%) were classified according to their reproductive capacity, in "reproductive conditions," 64%, and "non-reproductive condition," 7,1%. Women who reported being hysterectomized or in menopause also answered the same questions. Therefore, they were included in the analysis (Table 2).

Table 2: Distribution of women aged 15-49 according to reproductive condition. Brazil, 2006

Women's reproductive condition	Estimate	95% confidence interval		number of un weighted cases
		Lower Limit	Upper Limit	
Total	100,0%	-	-	15.575
Pregnant women	4,2%	3,6%	4,8%	588
Sterilized women	21,5%	20,4%	22,8%	4.096
Vasectomized partners	3,2%	2,8%	3,8%	361
Non-pregnant, non-sterilized, and women without vasectomized partners	71,1%	69,7%	72,4%	10.530
Women in reproductive conditions	64,0%	63,1%	65,8%	9.704
*Women in non-reproductive conditions**	7,1%	5,5%	7,9%	826

*Source: PNDS 2006. Note: *Women declared infertile, with difficulty getting pregnant, hysterectomized, or menopausal.*

Table 3 shows that the reproductive condition of women did not differ concerning its distribution in terms of skin color (p = 0.6032), socioeconomic status (p = 0.5756), and region (p = 0.6431). Regarding age, 58.1% of women in non-reproductive conditions were between 40 and 49 years old, while this percentage was 13.8% among women in reproductive conditions. The proportion of married/united women in non-reproductive conditions was higher (75.1%) than the other group (54%). As expected, the percentage of women without biological children was higher in the group of women in non-reproductive conditions (51.8%). Cramer's V permits affirming that there is a significant association between the non-reproductive condition and the women's age group. On the other hand, the relation of the non-reproductive condition with the marital status or the presence of biological children is relatively small, although significant.

Table 3: Distribution of women according to reproductive conditions bysociodemographic characteristics. Brazil, 2006

Characteristics	Non-Pregnant, Non-Sterilized Women Without Vasectomized Partners		Total	Number of Unweighted Cases
	In Reproductive Conditions	In Non-Reproductive Conditions*		
Race/color	*100,0%*	*100,0%*	*100,0%*	*10.442*
Not black	47,3%	45,6%	47,1%	4.810
black	52,7%	54,4%	52,9%	5.632
non-respondent				88
χ2= 0,94 (p= 0,6032)			Cramer's V	0,009
Socioeconomic status (SES)	*100,0%*	*100,0%*	*100,0%*	*10.486*
A	3,2%	1,7%	3,1%	304
B	21,2%	20,7%	21,1%	1.949
C	45,6%	47,1%	45,8%	4.896
D	22,7%	22,2%	22,6%	2.449
E	7,3%	8,4%	7,4%	888
non-respondent				44
χ2= 7,99 (p=0,5756)			Cramer's V	0,028
Age group	*100,0%*	*100,0%*	*100,0%*	*10.530*
15 - 24 years	44,7%	11,3%	41,6%	4.605
25 - 34 years	31,4%	13,6%	29,8%	3.242
35 - 39 years	10,1%	17,1%	10,8%	1.052
40 - 49 years	13,8%	58,1%	17,9%	1.631

χ2= 1.341,41 (p< 0,0001)			Cramer's V	0,357
Region	*100,0%*	*100,0%*	*100,0%*	*10.530*
North	6,4%	6,9%	6,4%	1.609
Northeast	25,0%	25,8%	25,0%	2.078
Southeast	45,7%	46,7%	45,8%	2.365
South	16,6%	14,3%	16,4%	2.535
Midwest	6,4%	6,3%	6,4%	1.943
χ2= 3,54 (p= 0,6431)			Cramer's V	0,018
Marital Status	*100,0%*	*100,0%*	*100,0%*	*10.521*
Single	36,2%	15,5%	34,3%	3.721
Married/United	54,0%	75,1%	56,0%	5.696
Widow / Separated / Divorced	9,8%	9,4%	9,7%	1.104
Non-respondent				9
χ2= 180,56 (p< 0,0001)			Cramer's V	0,131
Presence of biological children	*100,0%*	*100,0%*	*100,0%*	*10.530*
No	43,0%	51,8%	43,9%	4.450
Yes	57,0%	48,2%	56,1%	6.080
χ2= 27,37 (p= 0,0016)			Cramer's V	0,051

*Source: PNDS 2006. Note: *Women declared infertile, with difficulty getting pregnant, hysterectomized, or menopausal.*

Table 4 shows that of the total number of women who declared they wanted children/more children, 5.7% were in non-reproductive conditions. However, only those who marked the answers "Infertile/Difficulty getting pregnant" or "Infertile husband" as a reason for not getting pregnant were directed by the questionnaire to answer the questions about seeking and accessing infertility treatment (Table 5).

Table 4: Distribution of women who want children/more children, according to reproductive conditions

Desire to have children/or more children	Estimate	Confidence interval 95%		Number of unweighted cases
		Lower limit	Upper limit	
Non-pregnant, non-sterilized women with no vasectomized partners	100,0%	100,0%	100,0%	10.530
Want to have children	100,0%	100,0%	100,0%	5.428
Women in reproductive conditions	94,3%	93,1%	95,2%	5.136
Women in non-reproductive conditions[1]	5,7%	4,8%	6,9%	292

*Source: PNDS 2006.Note: *Women declared infertile, with difficulty getting pregnant, hysterectomized, or menopausal.*

Table 5 indicates that just under half of them did not seek help (49,1%), while about 28% were waiting, not receiving care, or thinking there was no solution. Almost half of those seeking help were undergoing treatment, 68.3% sought SUS, and 20.3% had health insurance. About 72% of the women who did not seek help indicated that the main reason was the lack of a solution to their problem or that they would not get it, while 26.8% cited financial reasons and 1,2% did not know where to get support.

Table 5: Distribution of infertile women/with difficulty conceiving/or infertile husbands who wish to have children by seeking infertility treatment. Brazil. PNDS 2006

Infertility treatment questions	Estimate	95% confidence interval		number of unweighted cases*
		Lower limit	Upper limit	
Did you seek help to get pregnant	100,0%	-	-	246
Yes, not answered	7,3%	2,6%	18,8%	14
Yes, waiting	7,9%	3,2%	18,2%	14
Yes, no solution	12,9%	8,2%	19,7%	35
Yes, under treatment	22,7%	15,1%	32,7%	54
Did not seek help	49,1%	39,3%	59,1%	129
Non-responders				6
Where did you look for help	100,0%	-	-	117

SUS	68,3%	55,3%	79,0%	66
Health insurance	20,3%	11,9%	32,5%	25
Private clinic/doctor	11,3%	6,6%	18,5%	25
Other	0,1%	0,0%	0,8%	1
What happened when you sought help to be able to get pregnant	100,0%	-	-	114
Waiting for service	4,3%	2,0%	9,2%	9
Answered: no solution	24,4%	14,9%	37,3%	32
Answered:No money for treatment	11,3%	5,9%	20,6%	15
Attended in treatment	48,5%	34,1%	63,2%	51
It has not been answered	11,5%	4,5%	26,2%	7
Non-responders				3
Reason for not seeking help (main reason)	100,0%	-	-	61
I think there is no solution	54,7%	37,5%	70,9%	29
I do not think I can get help	17,3%	7,1%	36,5%	9
I do not know where to get it	1,2%	0,2%	7,5%	2
I do not have money	26,8%	15,3%	42,8%	21
non-responders				68

*Source: PNDS 2006. Note: *Women who answered questions about seeking care in health services.*

Table 6 illustrates the distribution of questions about seeking infertility treatment according to sociodemographic characteristics. The results show that black women have the least desired medical care (58.7%) compared to non-black women (37.6%). The percentages of women from classes D and E who did not seek support are also high, 69.6% and 92.2%, respectively. Women at the extremes of the age group had the highest percentages of non-demand (55.9% between 15 and 24 years and 60.9% between 40 and 49 years). Regarding residency status, the North region had the highest non-demand proportion (74.1%), followed by the Midwest (68.2%) and Northeast (65.2%); in the South and Southeast regions, this percentage reached the lowest level, 30,7%, and, 39,1%, respectively. Cramer's V indicated that the sociodemographic characteristics most associated with seeking help to get pregnant are socioeconomic status, region, and race, in this order. The relation between seeking help to get pregnant and age group was insignificant ($p > 0.05$).

Table 6: Distribution of infertile women/with difficulty conceiving/or infertile husbands who wish to have children by socio-demographic characteristics, by demand for infertility treatment. Brazil, 2006

Sociodemographic characteristics	Sought help to get pregnant*		Total	Number of unweighted cases
	Yes	No		
Race/color	50,8%	49,2%	100%	244
Not black	62,4%	37,6%	100%	112
Black	41,3%	58,7%	100%	132
Non-responders				8
χ2= 10,75 (p= 0,0225)			Cramer's V	0,210
Socioeconomic status	50,8%	49,2%	100%	245
A	61,2%	38,8%	100%	3
B	83,3%	16,7%	100%	32
C	60,9%	39,1%	100%	118
D	30,4%	69,6%	100%	66
E	7,8%	92,2%	100%	26
Non-responders				7
χ2= 46,37 (p< 0,0001)			Cramer's V	0,435
Age group	50,9%	49,1%	100%	246
15-24 years	44,1%	55,9%	100%	32
25-34 years	55,8%	44,2%	100%	77
35-39 years	68,7%	31,3%	100%	48
40- 49 years	39,1%	60,9%	100%	89

Non-responders				6
χ2= 14,87 (p= 0,0767)			Cramer's V	0,246
Region	50,9%	49,1%	100%	246
North	25,9%	74,1%	100%	49
Northeast	34,8%	65,2%	100%	46
Southeast	69,3%	30,7%	100%	48
South	60,5%	39,5%	100%	46
Midwest	31,8%	68,2%	100%	57
Non-responders				6
χ2= 30,32 (p= 0,0023)			Cramer's V	0,351

*Source: PNDS 2006. Note: *Considering only women declared infertile, with difficulty getting pregnant, hysterectomized, or menopausal.*

IV. Discussion

This study identified and characterized women of reproductive age who self-reported infertility, their desire to have children, and demands for treatment from a socio-demographic point of view. The adopted definition of infertility as "self-declared" was based on women's reports about infertility or difficulty in conceiving. This approach aligns with other demographic research that considers the inclusion of self-reported perceptions of infertility as one of the possibilities for inferring the potential demand for health services (Dick et al., 2003[8]; Larsen, 2005[9];Cabrera-León et al., 2015)[11].

Nonetheless, we must consider that this declaration was made at a certain point in her personal or family life cycle. Transitions over time also lead to changes in desires regarding reproductive life. Therefore, this preliminary study can be seen as a demographic picture of the situation at a given time frame. In this sense, the percentage of self-reported infertility, 7.1%, and the rate of those who wish to have children or more children, 5.7%, can be understood as an approximation of the potential demand for infertility treatments.

However, not all women who meet the medical criteria for infertility indicate that they are trying or want to have a baby, which suggests that some infertile women do not need treatment. Without a desire for children, it is impossible to know if all women who declared themselves infertile see it as a problem to be solved (Greil et al., 2016)[11].

Our study found that almost half of the women in non-reproductive conditions who want to have children did not seek help from health services, while others sought help but were not answered. Women who seek medical services differ in respect from those who do not–higher income, residents in the Southeast and the South regions of the country, and not black. This could imply a gap in the healthcare system or a lack of awareness among individuals regarding available treatment options. The demand for care in health services is an essential indicator for women to be adequately diagnosed and referred for treatment.

Our findings are consonant with studies that suggest that while there is a global demand for infertility treatment, socioeconomic factors, limited access to services, and high costs contribute to social inequality in access to infertility treatments, among various factors contributing to this situation (Passet-Wittig & Greil, 2021[12]; Chambers et al., 2019[13]; Datta et al., 2016[14]; Cabrera-León et al., 2015[10], Boivin et al., 2007)[15]. The patterns observed in these studies seem consistent, indicating that individuals with higher socioeconomic status or educational qualifications are more inclined to seek assistance for fertility-related issues.

Data from PNDS 2006 provides valuable insights into the socioeconomic strata, race of women, and regional disparities and their association with seeking help to get pregnant. Limited access to healthcare facilities, either due to geographic factors or lack of healthcare infrastructure in specific communities, can also contribute to inequalities in reproductive health.

As seen in this work, women of color and women with low socioeconomic status are worse off. Racial and ethnic disparities in healthcare access and outcomes have been documented in numerous studies. These disparities often stem from a complex interplay of social, economic, and systemic factors. This highlights the intersectionality of race and socioeconomic status, indicating that being poor may exacerbate the challenges faced by black women in accessing reproductive health services. There is a potential for racial discrimination in access to reproductive health actions. This is a critical point, as bias can manifest in various ways, from unequal treatment in healthcare facilities to disparities in the quality of care. Milanezi (2024)[16] points to the discriminatory experiences of black women in the SUS bureaucracies in Rio de Janeiro. In light of literature produced by qualitative studies on health inequality, it is a plausible hypothesis that discriminatory experiences may have a bearing on the lower demand by the poorest and black women for infertility treatment in the health system.

More studies on this topic must be conducted in Brazil, and appropriate data should be collected regularly. This underscores the importance of further research to understand the dynamics of fertility help-seeking behavior in this population. Lack of awareness

or information about reproductive health issues and available services can also contribute to delayed or insufficient care. It is crucial to ensure that individuals are informed about the importance of seeking help early and know where to access specialized care.

Table 7 summarizes the information available in each of the population surveys carried out in Brazil that address the issue of human sterility in some way.

Chart 1: Information was collected by the National Demographic Survey (PNDS) in 2006 and 2023 and the National Health Survey (PNS) in 2013 and 2019

Information	PNDS 2006	PNDS 2023	PNS 2013	PNS 2019
Female fertility	Yes	Yes	No	No
Number of biological children of the woman	Yes	Yes	No[a]	No[a]
Pregnant woman	Yes	Yes	Yes	Yes
Woman with difficulty getting pregnant	Yes	Yes	No[b]	No[b]
Sterilized woman	Yes	Yes	Yes	Yes
Woman declared infertile	Yes	Yes	No	No
Hysterectomized woman	Yes	Yes	Yes	Yes
Menopausal woman	Yes	Yes	Yes	Yes
Vasectomized partner	Yes	Yes	Yes	Yes
Partner declared infertile	Yes	No	No	No
Desire to have children or more children	Yes	Yes	No	No
Sought help to get pregnant	Yes	No	No[b]	No[b]
Where the woman looked for help	Yes	No	No	No
What happened when the woman sought help to be able to get pregnant	Yes	No	No	No
Reason for not seeking help (main reason)	Yes	No	No	No

Source: Self-elaboration is needed considering the survey questionnaires. Note: a. The PNS counts the number of parturitions but does not specify if the product of that parturition was a living child or a dead child. b. The survey investigates if the woman or the partner has already taken or is taking any treatment to get pregnant. Certainly, someone with difficulty getting pregnant can never seek help.

In Brazil, family planning is often automatically associated with contraception, that is, the distribution of contraceptive methods, including tubal ligation and vasectomy. The other side of family planning and conception needs more effective actions by the public Unified Health System (SUS). The statistical system tends to reproduce this silence and bias. All data collected about reproductive health after 2006 did not evaluate if the women sought help to get pregnant, where, what happened when they sought help to be able to get pregnant, and the reason indicated by those women who preferred not seeking help. More than just counting the infertile women or men, public health policymakers need to know their perceptions and experiences with the services. This situation highlights a common challenge in healthcare systems, particularly reproductive health. While the SUS in Brazil, for example, emphasizes primary care as the initial point of contact for addressing infertility, barriers to accessing specialized services can impede the system's effectiveness (Berquó, Lago & Garcia, 2023)[17]. Although comprehensive assistance to women's health encompasses education actions that inform about fertility, infertility, and access to infertility treatments in the public network, its full effectiveness, as agreed at the Cairo Conference in 1994, has not been implemented by Brazilian governments since then.

V. Limitations

The limitations of the study are recognized. Firstly, as infertility/difficulty in conceiving is based on self-declaration, it is impossible to determine whether this condition was based on medical diagnosis, what type of infertility (primary or secondary), and how long it has been present. Secondly, opinions are restricted to the moment of the interview. In this sense, the statement about the desire for children may shift depending on the future of the interviewee's situation.

Despite the methodological restrictions mentioned, the study has the merit of bringing essential issues related to recognizing infertility as a health problem with severe implications for the individual and society.

VI. Conclusions

Addressing these challenges may involve a multi-faceted approach, such as Expanding the healthcare infrastructure, especially in underserved

areas, which can help ensure that specialized services are more widely available; implementing policies or programs that provide financial assistance or coverage for infertility treatments can make these services more accessible to a broader population. The emphasis on improving access to fertility diagnoses and treatments in public health services is crucial. Ensuring that a more significant segment of the population has access to these services is vital for upholding reproductive rights and addressing the broader societal implications of infertility.

The absence of systematic data on the causes and prevalence of both female and male infertility in Brazil is a significant concern. Understanding the root causes and extent of infertility is crucial for developing effective public health policies and interventions. Investing in research and data collection is essential to understanding the current landscape and tracking changes over time.

The call for including critical questions about infertility, access, and perceptions about the available services in the upcoming PNDS and PNS is crucial for gaining a deeper understanding of the affected population and the types of infertility they experience. This information can serve as a foundation for developing targeted public policies and programs to address the challenges faced by individuals dealing with infertility.

In conclusion, there is a compelling call to action for the State to prioritize addressing infertility issues in Brazil, recognizing the urgency of the matter, and emphasizing the potential consequences for the population. It highlights the need for proactive measures, including data collection, policy development, and improved access to fertility services, to address the multifaceted aspects of infertility and promote reproductive health and rights.

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Urinary Tract Infections During Pregnancy: Prevalence, Risks and Treatment

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Abstract- The article discusses the high incidence and risks of urinary tract infections (UTIs) in pregnant women. Due to physiological and anatomical changes during pregnancy, such as the dilation of the urinary tract and compression of the ureters, the risk of UTIs increases significantly. UTIs can be asymptomatic, present as cystitis, or progress to pyelonephritis, each with its own complications and treatment needs. The main complications associated with UTIs in pregnancy include preterm birth, low birth weight, anemia, renal insufficiency, and systemic infection, affecting both the mother and the newborn. The article emphasizes the importance of early screening and treatment to prevent these complications, recommending urine culture tests at the beginning and throughout pregnancy. Treatment should be based on the efficacy and safety of antibiotics for the fetus, with penicillins and cephalosporins being the first-line medications.

Keywords: urinary tract infections; pregnancy; asymptomatic bacteriuria; cystitis; pyelonephritis; complications; risks; treatments.

GJMR-E Classification: NLM: WQ330, WQ450

Strictly as per the compliance and regulations of:

Urinary Tract Infections During Pregnancy: Prevalence, Risks and Treatment

Infecções do Trato Urinário na Gestação: Prevalência, Riscos eTratamento

Natalia Rincon Arruda Daguer Damasceno [α] & Lorena de Sousa Ciriaco [σ]

Resumo- O artigo discute a alta incidência e os riscos das infecções do trato urinário (ITUs) em gestantes. Devido às alterações fisiológicas e anatômicas durante a gravidez, como a dilatação do trato urinário e a compressão dos ureteres, o risco de ITUs aumenta significativamente. As ITUs podem ser assintomáticas, apresentar-se como cistite ou evoluir para pielonefrite, cada uma com suas próprias complicações e necessidades de tratamento. As principais complicações associadas às ITUs na gestação incluem parto prematuro, baixo peso ao nascer, anemia, insuficiência renal e infecção sistêmica, tanto para a mãe quanto para o recém-nascido. O artigo destaca a importância do rastreamento e tratamento precoce para prevenir essas complicações, recomendando exames de urocultura no início e durante a gestação. O tratamento deve ser baseado na eficácia e segurança dos antibióticos para o feto, sendo as penicilinas e cefalosporinas os medicamentos de primeira linha. A prevenção, rastreamento e tratamento adequado das ITUs são essenciais para reduzir os riscos de desfechos adversos na gravidez. Adicionalmente, é fundamental que novos estudos sejam realizados para aprofundar a compreensão da relação entre ITUs e as complicações para o feto, como baixo peso ao nascer e prematuridade, que ainda hoje não está completamente definida.

Palavras-chave: infecções do trato urinário; gestação; bacteriúria assintomática; cistite; pielonefrite; complicações; riscos; tratamento.

Abstract- The article discusses the high incidence and risks of urinary tract infections (UTIs) in pregnant women. Due to physiological and anatomical changes during pregnancy, such as the dilation of the urinary tract and compression of the ureters, the risk of UTIs increases significantly. UTIs can be asymptomatic, present as cystitis, or progress to pyelonephritis, each with its own complications and treatment needs. The main complications associated with UTIs in pregnancy include preterm birth, low birth weight, anemia, renal insufficiency, and systemic infection, affecting both the mother and the newborn. The article emphasizes the importance of early screening and treatment to prevent these complications, recommending urine culture tests at the beginning and throughout pregnancy. Treatment should be based on the efficacy and safety of antibiotics for the fetus, with penicillins and cephalosporins being the first-line medications. Prevention, screening, and adequate treatment of UTIs are essential to reduce the risks of adverse pregnancy outcomes. Additionally it is crucial that new studies be conducted to deepen the understanding of the relation between UTIs and complications for the fetus, such as low birth weight and prematurity, which are still not fully defined.

Keywords: urinary tract infections; pregnancy; asymptomatic bacteriuria; cystitis; pyelonephritis; complications; risks; treatments.

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I. Introdução

A infecção do trato urinário (ITU) é definida pela presença de bactérias no trato urinário, capazes de causar alterações morfológicas e/ou funcionais. Em gestantes, o risco de ITU aumenta devido a modificações fisiológicas e anatômicas (HERRAIZ et al., 2005). No início da gestação, altos níveis de progesterona promovem uma ação miorrelaxante, favorecendo a dilatação pielocalicinal e ureteral e a diminuição do peristaltismo no trato urinário. A partir da sétima semana, 90% das gestantes apresentam dilatação do trato urinário superior, com pico entre a 22ª e 24ª semana. Além disso, a compressão extrínseca dos ureteres pelo útero gravídico e a dilatação do plexo venoso ovárico contribuem para a hidronefrose fisiológica da gestação (SILVA et al., 2018). O esvaziamento incompleto da bexiga facilita o refluxo e a migração bacteriana ascendente (HERRAIZ et al., 2005).

A ITU em gestantes resulta da combinação de fatores predisponentes com a virulência dopatógeno. A infecção pode ocorrer via hematogênica, linfática ou ascendente, sendo esta última a principal. A uretra feminina, relativamente curta (3 a 4 cm), facilita a contaminação, especialmente por bactérias como Escherichia coli, que possuem fímbrias para aderência ao urotélio (SILVA et al., 2018). Estima-se que até 20% das mulheres grávidas sofram de ITU, com 10% necessitando de internação. ITUs são a segunda enfermidade mais comum em gestantes, após a anemia (SILVA et al., 2018).

A ITU na gestação pode ser classificada em: bacteriúria assintomática (BA), cistite (ITU baixa) e pielonefrite (ITU alta). A BA não apresenta sintomas clínicos e pode ser diagnosticada por exames de rastreamento no pré-natal, permitindo tratamento

precoce e evitando a progressão para pielonefrite (SILVA et al., 2018). A cistite causa sintomas como polaciúria, disúria, urgência miccional, hematúria e dor em baixo ventre. A pielonefrite, caracterizada pela inflamação no parênquima e pelve renal, apresenta bacteriúria significativa e manifestações sistêmicas como febre, lombalgia, náuseas, vômitos e prostração, além de sinal de Giordano positivo, podendo ou não se manifestar com os sintomas clássicos de cistite. Cistite e pielonefrite podem acometer entre 1% a 4% das gestantes (SILVA et al., 2018).

A urocultura é o exame padrão ouro para rastreamento e diagnóstico. Na ausência deste, o exame de urina de rotina com piúria e o teste do nitrito e leucócito-esterase positiva auxiliam no diagnóstico e permitem o tratamento empírico (FILHO; D'ABREU, 2021). A incidência de BA em gestantes é de 2% a 10%, e as complicações das ITUs incluem parto prematuro, amniorrexe prematura, baixo peso ao nascer, anemia, insuficiência renal, hipertensão arterial e infecção sistêmica materna e neonatal, justificando o rastreamento rotineiro no pré-natal com exames de EAS e urocultura no primeiro e terceiro trimestres (SILVA et al., 2018).

Dada a prevalência, riscos e complicações das ITUs na gestação, a prevenção, rastreamento e tratamento adequado são fundamentais para reduzir o risco de desfechos graves. Este estudo visa analisar as evidências científicas sobre a prevalência das ITUs na gestação, seus possíveis riscos para mãe e feto, e o tratamento recomendado para cada tipo de afecção (Bacteriúria Assintomática, Cistite e Pielonefrite). Objetivos específicos incluem identificar a população de risco para ITU na gestação, avaliar a eficácia do rastreamento para BA em gestantes e relacionar a ITU na gestação com a incidência de parto prematuro e baixo peso ao nascer.

II. Metodologia

Este estudo é uma revisão narrativa de literatura, cujo objetivo principal é analisar a prevalência, os riscos e o tratamento adequado da infecção urinária durante a gestação. A pesquisa foi realizada nas bases de dados UptoDate, MedLine, SCielo e Cochrane, além de livros de Medicina de Emergência e Ginecologia e Obstetrícia. Utilizou-se os descritores "urinary tract infection" e "pregnant woman".

Os critérios de inclusão foram: artigos e bibliografias relevantes ao tema, publicados entre 1995 e 2021, em inglês, português ou espanhol, com texto completo disponível em formato eletrônico e que apresentavam evidências e teorias sólidas sobre o assunto. Os critérios de exclusão foram: bibliografias desatualizadas ou inespecíficas, artigos incompletos, de baixa relevância científica ou com resultados tendenciosos.

Os trabalhos selecionados foram lidos na íntegra, analisados e criticamente revisados para compor o conteúdo deste estudo. Após aplicar os critérios de inclusão e exclusão, 16 artigos foram selecionados.

III. Revisão de Literatura

a) *Epidemiologia e Classificação das Infecções do Trato Urinário na Gestação*

Silva e colaboradores (2018) afirmam que a Infecção do Trato Urinário (ITU) é a principal forma de infecção durante a gravidez. Estas ocorrem entre 17% a 20% das gestações e pode levar a complicações, tais como a corioamnionite clínica e subclínica, parto prematuro e infecção neonatal; além de insuficiência respiratória, distúrbio eletrolíticos, insuficiência renal, choque séptico e morte, que constituem complicações maternas graves (VAZQUEZ, J.C; ABALOS, E., 2011).

De acordo com Szweda e Józwik (2016), as ITUs compõem a segunda doença mais comum da gestação, sendo a causa de aproximadamente 5% das internações hospitalares na prenhez. Nesse sentido, devido à alta morbimortalidade materna e neonatal, Malta e colaboradores (2014) preconizam que diagnóstico e tratamento precoces são essenciais para evitar desfechos adversos epossíveis complicações.

A ITU na gestação é classificada em três variações: Bacteriúria Assintomática (BA), Cistite e Pielonefrite. Millar e Cox (1997) em seu estudo, definem a BA como a colonização de bactérias de forma persistente no trato urinário, com ausência de sintomatologia clínica, e está presente em cerca de 10% das gestantes. Tem como fator de risco o baixo nível socioeconômico, traço falciforme e Diabetes Mellitus (DM), inclusive a DM gestacional (GILSTRAP, L. C.; RAMIN, S.M., 2001).

Caso não seja tratada, a BA evolui para pielonefrite aguda em aproximadamente 30% das mulheres grávidas. Neste cenário, Romero e colaboradores (1989) desenvolveram uma metanálise na qual demonstrou que gestantes sem bacteriúria apresentavam metade do risco de parto prematuro, em comparação com as gestantes que apresentaram BA não tratada durante a gravidez. Este estudo também constatou que mulheres sem bacteriúria na gravidez apresentaram um risco significativamente menor de terem um bebê com baixo peso ao nascer, quando comparado às gestantes com BA sem tratamento. Sendo assim, apesar de a relação entre a BA e a prematuridade e o baixo peso ao nascer seja um motivo de controvérsia atualmente, pode-se dizer que existe uma associação e, por esse motivo, as gestantes rastreadas com BA no início da gravidez devem ser tratadas com antibioticoterapia.

Conforme Glaser e Schaeffer (2015) citam em seu trabalho, é recomendado o rastreio para BA pela urocultura no início da gestação e outros, entre a 12ª e 16ª semanas. A urocultura continua sendo o método mais eficaz para rastreio de BA, mesmo com sua a demanda de tempo – uma vez que necessita de um período de 24 a 48 horas de análise – e o alto custo. Outros testes, como a urinálise e a tira reagente de urina não apresentam sensibilidade significativa para a bacteriúria (GLASER, A.; SCHAEFFER, A., 2015).

De acordo com Filho e colaboradores (2018) e Duarte e colaboradores (2008) a cistite apresenta-se com sintomas de infecção do trato urinário baixo, tais como disúria, polaciúria, hematúria e dor em baixo ventre e é definida pela colonização bacteriana na mucosa vesical. Atualmente, a cistite bacteriana apresenta o desconforto como única morbidade relacionada à gestação (MILLAR, L. K.; COX, S.M., 1997).

Já a pielonefrite, segundo Ángel Herráiz e colaboradores (2005), é a principal causa não obstétrica de internação em mulheres grávidas e deve ser considerada como uma complicação grave, uma vez que está estritamente associada ao choque séptico, trabalho de parto prematuro e retardo do crescimento intrauterino.

> "É mais comum no segundo (45-50%) e terceiro trimestres (40-45%) do que no primeiro (10%). O risco de recorrência durante a mesma gravidez é de 15%. Quase um terço das mulheres grávidas com PA terá infecções recorrentes e/ou anormalidades estruturais dos rins no futuro. Por esse motivo, é necessário realizar um acompanhamento com uroculturas semelhante à proposta para BA. Em Pielonefrite recorrente ou com complicações urológicas, as pacientes devem ser reavaliadas no pós-parto." (ÁNGEL HERRÁIZ, M. et al., 2005, p. 44).

De acordo com Glaser e Schaeffer (2015), os principais fatores de risco para pielonefrite na gestação são: presença de BA, nulíparas, episódios anteriores de pielonefrite, doença ou traço falciforme, diabetes, imunossuprimidas e com idade mais jovem.

b) Etiologia das Infecções do Trato Urinário na gravidez

Os uropatógenos mais comumente isolados na BA são similares àqueles encontrados na cistite e na pielonefrite, sendo a *Escherichia coli* o principal patógeno. Outros patógenos podem ser encontrados, como: *Enterobacter sp.*, *Proteus Klebsiella sp.*, *Pseudomonas sp.*, *Staphylococcus saprophyticus*, *Enterococcus faecalis* e *Streptococcus agalactiae* (grupo B) (FILHO; D'ABREU, 2021).

A maior incidência etiológica pela E. Coli pode ser explicada, segundo Ángel Herráiz e colaboradores (2005) pela menor produção de interleucina-6 pela gestante e consequente queda na resposta antigênica específica ao patógeno.

Filho e colaboradores (2021) afirmam que a *E. Coli* seja responsável por 75% a 90% dos casos. O mesmo trabalho também cita outros patógenos gram-negativos relacionados à ITU, tais como *Klebsiella pneumoniae, Proteus mirabilis, Enterococcus* e *Enterobacter;* além de gram-positivos, como o *Streptococcus agalactiae* ou estreptococo do grupo B, agente destacado pelo estudo de Allen e colaboradores (2012) por sua significância na prevalência de desfechos adversos, casonão tratada.

c) Tratamento

A revisão sistemática de Vazquez e Abalos (2011) reuniu diversos ensaios clínicos randomizados com o objetivo de determinar o tratamento mais efetivo para as ITUs na gestação. Segundo os autores, a escolha da antibioticoterapia deve se basear nos seguintes fatores: eficácia do medicamento, sua cobertura contra o patógeno, sua capacidade de manter níveis séricos e teciduais durante o período de tratamento, além de seu custo, tolerância e segurança para o feto. Neste estudo, os agentes microbianos listados foram:

- Penicilinas e ampicilinas;
- Cefalosporinas (cefazolina e ceftriaxona);
- Aminoglicosídeos (gentamicina);
- Antimetabólicos (trimetoprima e sulfametoxazol) e
- Outros (nitrofurantoína, fosfomicina e trometamol).

Glaser e Schaeffer (2015) também discorrem acerca da escolha do tratamento a ser utilizado, enfatizando a segurança do mesmo para a mãe e para o feto. Segundo os autores, deve-se levar em consideração que algumas alterações fisiológicas da gestação podem modificar a farmacocinética no que diz respeito à concentração sérica do fármaco no organismo, uma vez que há aumento do volume intra e extravascular. Além disso, é importante ressaltar também que grande parte dos antimicrobianos são capazes de transpassar a placenta, causando teratogenicidade.

Os autores separaram os antibióticos mais comumente utilizados nas ITUs durante a gestação e os classificaram conforme às categorias A, B, C, D e X da Food and Drugs Administration (FDA). Os medicamentos da categoria A foram estudados em estudos controlados em gestantes, não apresentando risco ao feto no primeiro trimestre de gestação. A categoria B inclui fármacos que foram testados em estudos com animais e não apresentaram riscos para estes, porém não foram feitos estudos em mulheres grávidas. A categoria C possui medicações que não possuem testes em animais, nem em humanos; ou que foram testadas em animais e apresentaram risco. Já os fármacos da categoria D demonstram evidência científica para risco fetal, todavia, seus benefícios podem justificar os riscos. Por fim, a categoria X

engloba drogas cuja evidência científica demonstra risco ao feto e não há qualquer benefício ao seu uso maior que o risco. Na tabela 1, estão listados os antibióticos que podem ser utilizados na gravidez:

Tabela 1: Antibióticos utilizados na gravidez

Droga	Categoria FDA	Comentários
Amoxicilina	B	
Cefalexina	B	Cefalosporina de 1ª geração
Cefuroxima	B	Cefalosporina de 2ª geração
Ceftriaxona	B	Cefalosporina de 3ª geração
Clindamicina	B	Comumente utilizada em casode alergia a penicilinas
Azitromicina	B	
Nitrofurantoína	B	Apenas para ITU baixa; risco de teratogenia controversa poranemia hemolítica em deficiência de G6PD no terceiro trimestre
Fosfomicina	B	Apenas para ITU baixa
Sulfadiazina	C	Evitar se houver outras
		opções
Vancomicina	B	Dados limitados
Gentamicina	C	Comumente utilizada na pielonefrite; potencial riscode nefrotoxicidade e ototoxicidade
Ciprofloxacino	C	Evitar na gestação
Tetraciclina	C	Evitar na gestação

Adaptado de: GLASER, Alexander P.; SCHAEFFER, Anthony J. Urinary tract infection and bacteriuria in pregnancy. Urologic Clinics, v. 42, n. 4, p. 547-560, 2015.

Em resumo, as penicilinas são utilizadas como tratamento de primeira linha para infecções por Estreptococos do grupo B (EGB); para pielonefrite, usam-se as cefalosporinas; para infecções do trato urinário baixo, o medicamento mais utilizado é a nitrofurantoína; e aminoglicosídeos (gentamicina) em associação com ampicilina para tratamento de pielonefrite por bacilos negativos (GLASER, A.; SCHAEFFER, A., 2015).

A Tabela 2 a seguir demonstra resumidamente a incidência, diagnóstico e tratamento para as 3 classificações de ITU na gestação.

Tabela 2: Incidência, diagnóstico, tratamento recomendado e acompanhamento de BA,Cistite e Pielonefrite

	Incidência (%)	Diagnóstico	Duração do tratamento(dias)	Acompanhamento
Bacteriúria Assintomática	2-10	Sem sintomas; Bacteriúria confirmada na urocultura.	3-7	Triagem periódicapara bacteriúria recorrente; Considerar antibioticoterapiaprofilática.
Cistite	1-2	Disúria; Urgência	3-7	Triagem periódicapara bacteriúria recorrente;
		miccional; Polaciúria; Hematúria; Desconforto suprapúbico; Bacteriúria.		Considerar antibioticoterapiaprofilática.
Pielonefrite	1	Febre; Calafrios; Dor nos flancos; Náuseas evômitos; Bacteriúria.	7-14	Triagem periódicapara bacteriúria recorrente; Considerarfortemente antibioticoterapiaprofilática.

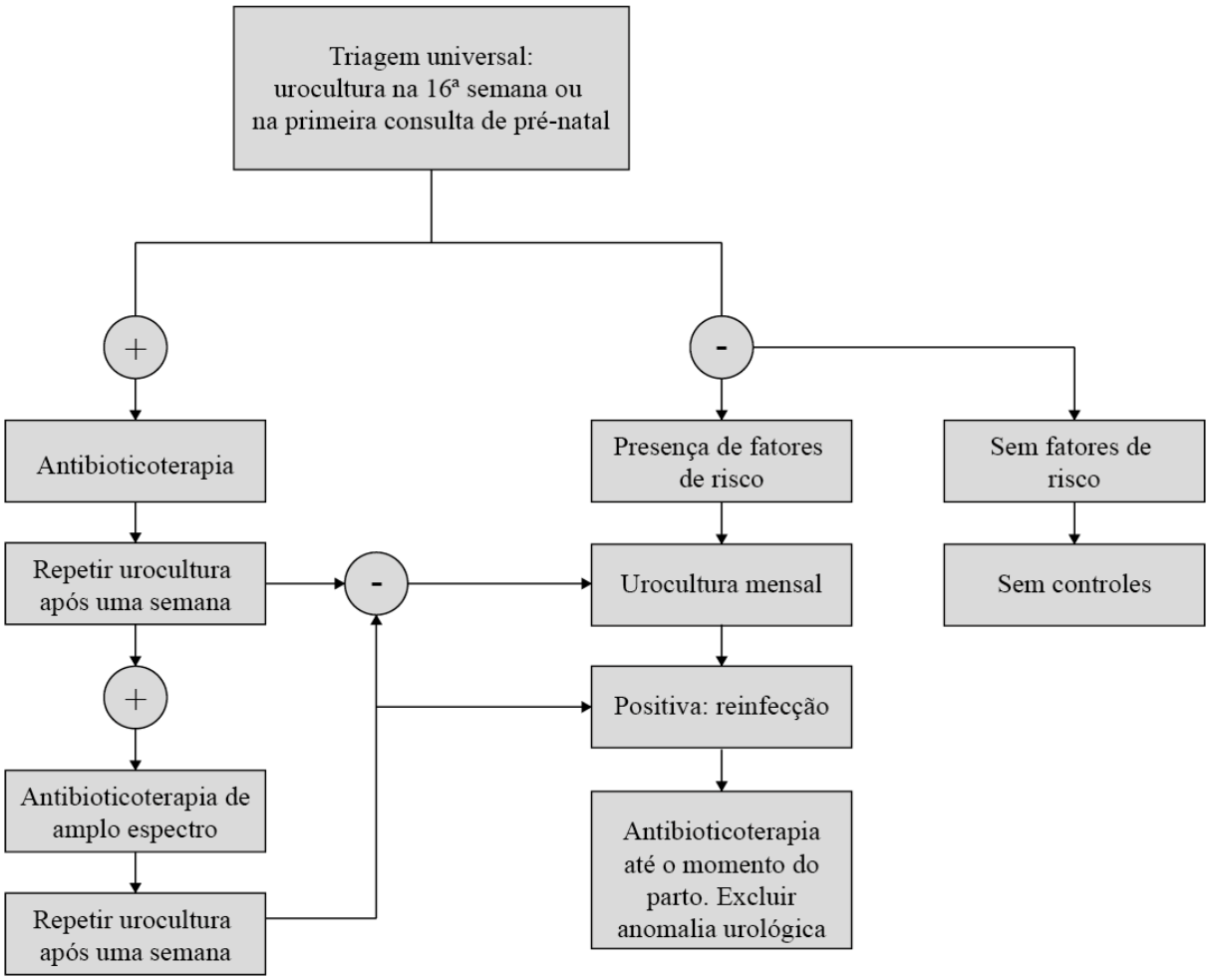
Adaptado de: GLASER, Alexander P.; SCHAEFFER, Anthony J. Urinary tract infection and bacteriuria in pregnancy. Urologic Clinics, v. 42, n. 4, p. 547-560, 2015.

i. *Bacteriúria Assintomática*

O tratamento da BA, de acordo com Filho e colaboradores (2021), deve ser ambulatorial por um período de 7 a 10 dias, seguido de uma posterior urocultura de controle, feita 7 dias após o término do tratamento. Já Silva e colaboradores (2018) preconizam o tratamento de curta duração, de 3 a 7 dias. Segundo os autores, a antibioticoterapia escolhida deve ser guiada pela sensibilidade apresentada na urocultura.

A *Infectious Diseases Society of America* (IDSA) recomenda que o tratamento para BA deve ser feito com fosfomicina em dose de 3g, via oral, por 3 a 7 dias (GLASER, A.; SCHAEFFER, A., 2015). Pode-se instituir também uma terapia profilática com 50 a 100 mg de nitrofurantoína diária, visto que cerca de um terço das pacientes tratadas para BA poderão desenvolver bacteriúria recorrente – mesma cepa com contagem significativa de colônias cultivadas dentro de 2 semanas após a conclusão do tratamento inicial – ou reinfecção – mesma ou diferente cepa comcontagem significativa de colônias por mais de 2 semanas após a conclusão do tratamento – , incluindo EGB, devem ser tratadas novamente com antibióticos sensíveis à cepa identificada (ALLEN, V. M. et al., 2012).

De acordo com Ángel Herráiz e colaboradores (2005), o tratamento da BA reduz a incidência de infecção sintomática em 80-90% dos casos, mas, em contrapartida, a probabilidade de recorrência após o tratamento é alta – até 30%. Neste cenário, recomenda-se a urocultura de gestantes diagnosticadas com BA uma semana após o tratamento – conforme descrito no fluxograma abaixo:



Adaptado de: ÁNGEL HERRÁIZ, M. et al. Infección del tracto urinario en la embarazada. Enfermedades Infecciosas y Microbiología Clínica, v. 23, p. 43, dez. 2005.

Figura 1: Fluxograma da Bacteriúria Assintomática

ii. *Cistite*

O tratamento empírico da cistite deve levar em consideração os dados microbiológicos anteriores da paciente e a segurança dos antimicrobianos na gestação. Segundo o Ministério da Saúde (apudSilva et al., 2018), para cistites não complicadas, as escolhas são: nitrofurantoína 100 mg, de 4 vezes ao dia, por 7 a 10 dias – com o cuidado de evitar após a 36ª semana

de gestação –; cefalexina 500 mg, no mesmo esquema; ou amoxicilina associada a clavulanato 500 mg, 3 vezes ao dia, também por 7 a 10 dias.

iii. *Pielonefrite*

Há uma discussão acerca do regime de tratamento para pacientes gestantes com pielonefrite. Para Glaser e Schaeffer (2015), o tratamento deve ser hospitalar e o antimicrobiano deve ser administrado via endovenosa.

A maioria dos autores afirmam que o regime de tratamento ideal para a pielonefrite em gestantes é hospitalar. Todavia, pelo alto custo, algumas pacientes podem ser eleitas ao regime ambulatorial e, segundo Gilstrap e Ramin (2001), estas devem preencher os seguintes critérios:

- Se possível, permanecer em observação por 23 horas;
- Ter tolerância aos medicamentos orais;
- Não apresentar sinais ou sintomas de choque séptico, nem de disfunção orgânica;
- Ter disponibilidade de acompanhamento domiciliar.

As pacientes que necessitarem de hospitalização, por outro lado, devem receber hidratação parenteral concomitante à antibioticoterapia, além da monitorização dos sinais vitais e do débito urinário.

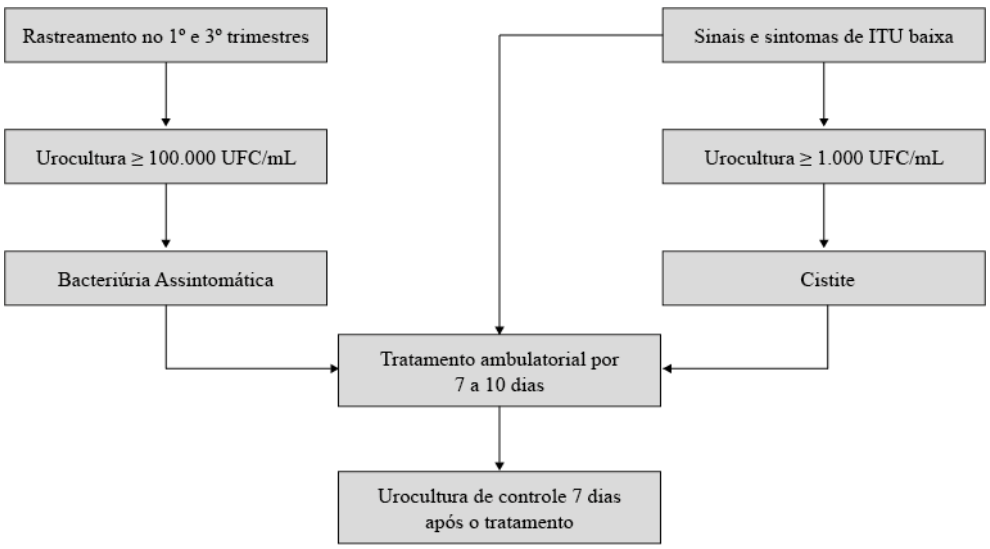
Silva e colaboradores (2018) e Filho e colaboradores (2021) afirmam que, por ser potencialmente grave, a pielonefrite deve ser tratada no ambiente intra hospitalar. Como um dos riscos é a infecção sistêmica e o choque séptico, é mandatório que os dados vitais da paciente sejam monitorados, além da verificação de necessidade de hidratação venosa e sintomáticos, como analgésicos e antieméticos. A terapia empírica deve ser iniciada precocemente, via endovenosa (EV), e alterada para via oral (VO), caso a gestante não apresente febre por no mínimo 48 horas. As drogas de escolha são: ampicilina e gentamicina, cefazolina, ambas EV; ou ceftriaxona, EV ouintramuscular (IM).

Caso a paciente não apresente cessação dos sintomas em 72 horas após início do tratamento empírico, deve-se considerar adicionar gentamicina ao esquema terapêutico, na dose de 3 a 5 mg/kg/dia, na justificativa de suspeita de patógeno resistente. Neste cenário, também é necessário investigar outros diagnósticos como a nefrolitíase e abscesso renal (GLASER, A.; SCHAEFFER,A., 2015).

Segundo Millar e Cox (1997), a disfunção renal, classificada com um clearance decreatinina menor que 80 mL/min, pode ocorrer em 25% das gestantes com pielonefrite e a tendência é que seja normalizada em poucos dias. Todavia, a administração de fluidos e a obtenção seriada de níveis séricos de creatinina devem ser feitos para acompanhamento e é importante se atentar ao tratamento com antibióticos que apresentem nefrotoxicidade nessas pacientes.

iv. *Fluxogramas para ITU baixa e ITU alta*

Filho e colaboradores (2021) organizaram a conduta de tratamento para as ITUs na gestação de acordo com o seu acometimento baixo (Bacteriúria Assintomática e Cistite) e alto (Pielonefrite).



Adaptado de: FILHO, Agnaldo Lopes da S.; D'ABREU, Bárbara F. Protocolos e condutas em ginecologia e obstetrícia. Rio de Janeiro: MedBook Editora, 2021. E-book. ISBN 9786557830789

Figura 2: Fluxograma de Infecções do Trato Urinário Baixo (BA e Cistite)

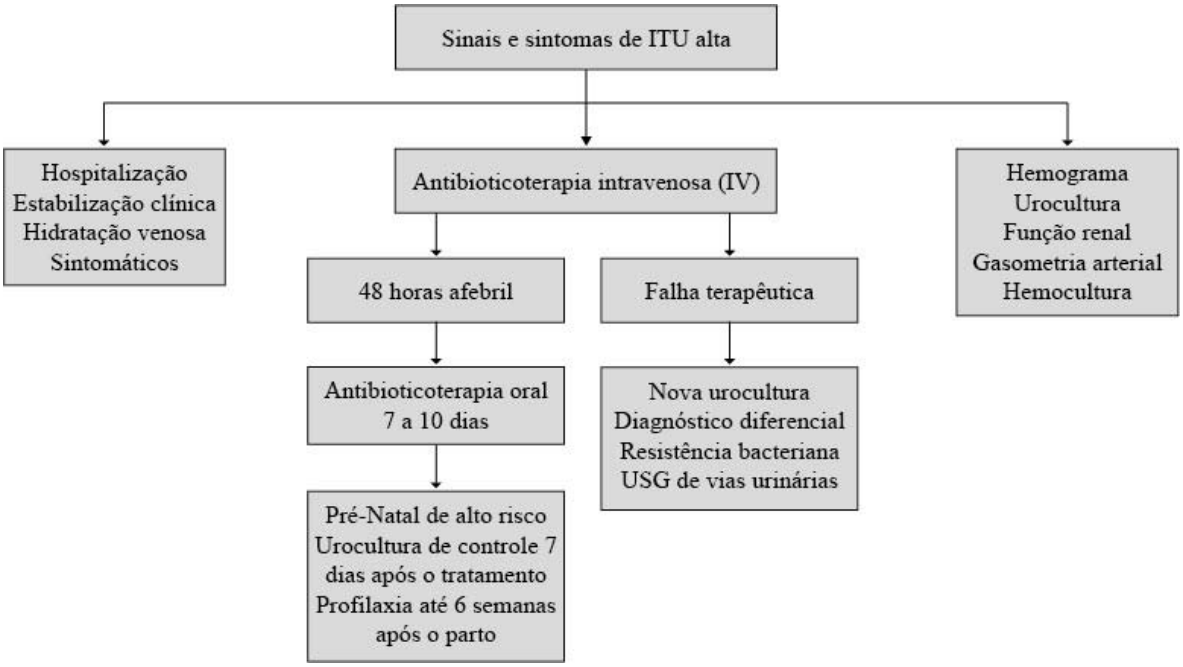


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Figura 3: Fluxograma de Infecções do Trato Urinário Alto (Pielonefrite)

v. *Resumo* do tratamento para BA, Cistite e Pielonefrite

A fim de sintetizar o que foi visto acerca do tratamento da ITU em gestantes no presente trabalho,a Tabela 5 abaixo apresenta os fármacos e os regimes de tratamento, de acordo com os autores analisados.

Tabela 5: Comparativo entre a escolha das terapias medicamentosas indicadas ao tratamento dasITUs ocorridas na gestação, pelos diferentes autores

Autor	Tipo de Infecção	Terapia Medicamentosa
Vazquez e Abalos (2011)	Pielonefrite	• Charleston, 1996: Antibióticos intravenosos +nitrofurantoína; • Flórida, 1995: Ceftriaxona ou cefazolina; • Los Angeles, 1998: Ceftriaxona IM OU ampicilina-gentamicina IV OU cefazolina IV.
Glaser e Schaeffer (2015)	Bacteriúria Assintomática	Penicilinas (Penicilina G, Amoxicilina, Ampicilina) – 3a 7 dias.
	ITU baixa (Cistite)	Nitrofurantoína e Aminoglicosídeos (gentamicina) – 3 a7 dias.
	Pielonefrite	Nitrofurantoína e Aminoglicosídeos (gentamicina) associada a Ampicilina (se bacilos negativos) – 7 a 14 dias.
Millar e Cox(1997)	Bacteriúria Assintomática	Nitrofurantoína, sulfisoxazole ou cefalexina – 3 a 7 diasou Nitrofurantoína, sulfisoxazole, cefalexina ouamoxicilina – dose única.
	ITU baixa (Cistite)	Nitrofurantoína, sulfisoxazole ou cefalexina – 3 a 7 diasou Nitrofurantoína, sulfisoxazole, cefalexina ouamoxicilina – dose única.
	Pielonefrite	Ampicilina IV + gentamicina IV;Cefazolina IV; Ceftriaxona IV;Mezlocilina IV;Piperacilina IV.
Gilstrap e Ramin (2001)	Pielonefrite	Cefalosporina ou ampicilina de primeira geração +gentamicina.
Herraiz (2005)	Bacteriúria Assintomática	Fosfomicina Trometamol – dose única.
	ITU baixa (Cistite)	Fosfomicina Trometamol – dose única.
	Pielonefrite	Amoxicilina/Ácido Clavulânico – 14 dias;Ceftriaxona – 14 dias; Cefuroxima Axetil – 14 dias. Se alergia à beta lactâmicos:Fosfomicina – 14 dias; Gentamicina ou Tobramicina – 14 dias;Aztreonam – 14 dias.

FEBRASGO - Tratado deObstetrícia (2019)	Bacteriúria Assintomática	Nitrofurantoína – 5 a 7 dias; Amoxicilina – 3 a 7 dias; Amoxicilina e Clavulanato – 3 a 7 dias;Cefalexina – 3 a 7 dias; Fosfomicina – 3 a 7 dias.
	ITU baixa (Cistite)	Nitrofurantoína – 5 a 7 dias; Amoxicilina – 3 a 7 dias; Amoxicilina e Clavulanato – 3 a 7 dias;Cefalexina – 3 a 7 dias; Fosfomicina – 3 a 7 dias.
	Pielonefrite	Ceftriaxona; Cefepime; Ampicilina e Gentamicina.
Filho e D'Abreu (2021)	ITU na gestação	Antibioticoterapia oral: • Amoxicilina – 7 a 10 dias; • Amoxicilina + clavulanato – 7 a 10 dias; • Ampicilina – 7 a 10 dias; • Cefalexina – 7 a 10 dias; • Nitrofurantoína – 7 a 10 dias; • Fosfomicina – dose única. Antibioticoterapia IV: • Amoxicilina + clavulanato – 8/8h; • Ceftriaxona – 24/24h; • Cefazolina – 8/8h; • Ampicilina – 6/6h; • Gentamicina – 24/24h.
Silva, Osonan,Bonomi (2018)	Bacteriúria Assintomática	Antibioticoterapia Oral: • Nitrofurantoína - 7 a 10 dias; • Cefalexina - 7 a 10 dias; • Amoxicilina + clavulanato - 7 a 10 dias.
	ITU baixa (Cistite)	Antibioticoterapia Oral: • Nitrofurantoína - 7 a 10 dias; • Cefalexina - 7 a 10 dias; • Amoxicilina + clavulanato - 7 a 10 dias.
	Pielonefrite	• Ampicilina + gentamicina EV – 24/24h; • Cefazolina endovenosa ou ceftriaxona endovenosa ou intramuscular.

vi. *Tratamento profilático em caso de recorrência*

Para a prevenção de ocorrência de ITU em gestantes, tem-se medidas farmacológicas e não farmacológicas. As farmacológicas consistem em antibioticoterapia profilática em mulheres com ITU recorrente, guiada pelo patógeno encontrado na última urocultura. Já para as medidas não farmacológicas, alguns estudos sugerem a suplementação de vitamina C para a população com alta recorrência de ITU e estudos com pouca evidência científica recomendam o uso de soluções em pó de *cranberry* (SILVA *et al*., 2018).

A profilaxia com antimicrobianos, de acordo com Filho e colaboradores (2021) deve ser ponderada para as mulheres grávidas com dois episódios de cistite ou um episódio de pielonefrite. Para estes casos, conforme relata Filho e colaboradores (2021), recomenda-se o uso de nitrofurantoína 100 mg por dia e cefalexina 500 mg por dia por um período de 6 semanas apósa concepção.

Conforme exposto, tanto o tratamento, quanto a profilaxia destinada às ITU na gestação são de suma importância para se evitar as possíveis complicações, advindas principalmente da pielonefrite, que são: "trabalho de parto prematuro e amniorrexe prematura, baixo peso ao nascer, anemia, insuficiência renal, hipertensão arterial e infecção sistêmica, tanto materna como neonatal" (SILVA et al., 2018). Vale ressaltar que, embora esta forma de acometimento seja a mais grave, qualquer que seja o diagnóstico inicial (BA ou cistite), deve-se tratar corretamente, com o intuito de evitar uma evolução para pielonefrite e, consequentemente, aumentar os riscos de complicações.

vii. *Complicações*

Conforme cita Gilstrap e Ramin (2001), cerca de 66% das gestantes com pielonefrite apresentaram anemia - definida com um hematócrito menor que 30%. A causa mais provável dessa complicação, segundo os

autores, é a hemólise secundária à endotoxina bacteriana.

Ángel Herráiz e colaboradores sintetizaram as principais complicações advindas da pielonefrite na gestação, listadas na Tabela 6.

Tabela 6: Complicações da Pielonefrite Aguda

Complicação	Frequência (%)	Considerações
Anemia hemolítica	25-30	Secundária a hemólise porendotoxinas; Hematócrito < 30% em dois terços dos casos.
Septicemia	15	Evolução para choqueséptico: 1-2%
Disfunção renal transitória	15-20	Creatinina < 80 mL/min Espera-se recuperação em algumas semanas com antibioticoterapia adequada.
Desconforto respiratórioagudo	5	Solicitar radiografia de tórax e gasometria arterial; 10-15% requerem ventilaçãomecânica.
Urinárias: • Abscesso perirenal; • Pielonefrite enfisematosa; • Litíase coraliforme.	< 5	Suspeitar se não houver resposta ao tratamento esolicitar ecografia renal.

Adaptado de: ÁNGEL HERRÁIZ, M. et al. Infección del tracto urinario en la embarazada. Enfermedades Infecciosas y Microbiología Clínica, v. 23, p. 40–46, dez. 2005.

Segundo Gilstrap e Ramin (2001), cerca de 15% dos bebês de mães que apresentaram pielonefrite na gestação tiveram peso ao nascer inferior a 2,5 kg.

> "Diversos patógenos que causam ITU produzem fosfolipase A2, o que culmina com a formação de prostaglandinas, como as prostaglandinas E2 e F2-alfa, que desencadeiam trabalho de parto prematuro e também podem ser a causa da rotura prematura de membranas. Esses mecanismos inflamatórios também são o motivo desse tipo de infecção aumentar em até 50% o risco de pré-eclâmpsia. O baixo peso ao nascer pode ser consequência do nascimento prematuro, mas também pode ser decorrente da infecção propriamente dita mesmo nos fetos nascidos a termo" (SILVA et al, 2018, p. 182).

Todavia, a associação de pielonefrite com o risco de parto prematuro e baixo peso ao nascer é controverso em todos os trabalhos analisados, uma vez que há um estímulo da atividade uterina com o uso de antibióticos na pielonefrite (GILSTRAP, L. C.; RAMIN, S. M., 2001).

IV. Considerações Finais

Tendo em vista que a ITU é uma das causas mais frequentes de internação das gestantes, torna-se essencial a reflexão acerca da prevalência, riscos e tratamento destas condições, além de realizar uma análise comparativa das diferentes condutas adotadas ao longo do tempo.

Diante do exposto, sabe-se que a realização de um exame físico de alta qualidade somado à urinálise são condutas padrão ouro para realizar o diagnóstico. A identificação do patógeno se torna essencial no que se diz respeito ao direcionamento do tratamento, visto que fatores como a eficácia do medicamento, sua cobertura contra o patógeno, sua capacidade de manter níveis séricos e teciduais durante o período de tratamento, além de seu custo, tolerância e segurança para o feto devem ser considerados no momento da escolha da terapia medicamentosa.

Visando atingir a realidade do SUS, a Federação Brasileira de Ginecologia e Obstetrícia (FEBRASGO) preconiza a utilização de Nitrofurantoína, Amoxicilina, Clavulanato, Cefalexina e Fosfomicina para o tratamento de Bacteriúria Assintomática e Cistite. No que se diz respeito à Pielonefrite, recomenda-se o uso de Ceftriaxona, Cefepime, Ampicilina e Gentamicina - terapias das quais mostraram-se eficazes na prevenção de complicações e morte. Sabe-se que, em diferentes países, as prescrições medicamentosas podem variar.

Por fim, a realização de ensaios clínicos com maior amostra possível de pacientes nos mais diversos países são indispensáveis para melhor nível de evidência sobre o tema, além de sua correlação com

possíveis riscos, tais como prematuridade e baixo peso ao nascer, haja vista que ainda hoje é controverso.

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Carboprost Versus Oxytocin in Active Management of Third Stage of Labour: Comparative Study

By Thakur NK, Shrestha B, Yadav BK, Aryal A & Shah C

Abstract- *Background:* Worldwide every one minute one woman dies from pregnancy or child birth related complications. This study attempt to compare efficacy of Carboprost versus Oxytocin for active management of third stage of labour.

Methodology: Three hundred obstetric cases anticipated for spontaneous vaginal delivery were randomly divided into two groups. Out of which 150 received Intramuscular oxytocin 10 units and 150 cases received Intramuscular Carboprost 125 µg after the delivery of the baby.

The main outcome measured with respect to outcome of third stage of labor were: duration, blood loss by volume, difference in hemoglobin, need for additional oxytocics and side effects.

Keywords: *oxytocin, carboprost and third stage of labour.*

GJMR-E Classification: *LCC: RG133.5*

Strictly as per the compliance and regulations of:

Carboprost Versus Oxytocin in Active Management of Third Stage of Labour: Comparative Study

Thakur NK [α], Shrestha B [σ], Yadav BK [ρ], Aryal A [ω] & Shah C [¥]

Abstract- Background: Worldwide every one minute one woman dies from pregnancy or child birth related complications. This study attempt to compare efficacy of Carboprost versus Oxytocin for active management of third stage of labour.

Methodology: Three hundred obstetric cases anticipated for spontaneous vaginal delivery were randomly divided into two groups. Out of which 150 received Intramuscular oxytocin 10 units and 150 cases received Intramuscular Carboprost 125 µg after the delivery of the baby.

The main outcome measured with respect to outcome of third stage of labor were: duration, blood loss by volume, difference in hemoglobin, need for additional oxytocics and side effects.

Results: Carboprost group had shown significant reduction in duration of third stage of labour ($p<0.001$), blood loss ($p<0.001$) and reduction in hemoglobin was also less when compared to oxytocin. Most of oxytocin group side effects like nausea and vomiting (6%) while diarrhea (12%) was common among carboprost group.

Conclusion: The study concludes that intramuscular carboprost 125 µg is more effective in active management of third stage of labour. However, a large metacentric randomized controlled trial is required to draw conclusion.

Keywords: oxytocin, carboprost and third stage of labour.

I. Background

Third stage of labour is the period from the delivery of the baby until the delivery of the placenta(1). Active management of third stage of labour involves; routine administration of a prophylactic uterotonic drug just before, with, or immediately after, the birth of the baby; early cord clamping and controlled cord traction to deliver the placenta(2). According to WHO the most common complication of third stage of labour is Postpartum hemorrhage (PPH) which is defined as a blood loss of at least 500ml after vaginal delivery and 1000ml after cesarean section and/or necessity of postpartum blood transfusion within 24hours of delivery(3,4).

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Drugs conventionally used for prophylaxis against PPH includes oxytocin, methylergotmetrin, carboprost and syntometrin(5). Among them Oxytocin acts through receptor and voltage mediated calcium channels to initiate myometrial contractions. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system (6). In other hand Carboprost It shortens induction to delivery interval. Carboprost being a prostaglandin promotes myometrium contraction irrespective of the duration of gestation, whereas oxytocin acts predominantly on the uterus at term or in labour.

The present study is an attempt to evaluate the scope of using carboprost tromethamine 125 µg which is half the therapeutic dose for PPH and to evaluate its efficacy in terms of amount of blood loss, duration of third stage, side effects in comparison with oxytocin 10 units in active management of third stage of labor.

II. Methodology

This study was a hospital based comparative study, conducted at National Medical College and Teaching

Hospital, Birgunj, Nepal which is a tertiary level hospital. The study period was twelve months from 16th July 2018 to 15th June, 2019. Ethical clearance was taken from institutional Review board (IRB) of National Medical College. Convenient Sampling method was used for sampling.

This study includes 300 women with singleton pregnancy with cephalic presentation in labor at term (3742 weeks of gestation). Excluding the women who underwent caesarean section, hypersensitivity to drugs, underlying comorbidity like respiratory diseases (asthma), cardiac disease, renal, liver disorder, epilepsy, psychiatry disorder, preeclampsia and eclampsia, severe anemia, multiple pregnancy, Polyhydramnios/ Oligohydramnios, Past History of PPH, Grand Multipara. These women are recruited in two group after taking informed consent with standardized form after admission in labor ward. Women who were likely to have vaginal delivery were offered entry to the trial with computer generated random numbers, to either control group to receive intramuscular oxytocin 10 units (group

A) or to the study group to receive intramuscular carboprost 125μg(group B) just after the delivery of the baby. A sterile tub is immediately placed at the vulva after delivery of fetus and blood volume was measured by measuring jar. Differences in the weight of drapes and sanitary pads was also estimated by weighing it before and after delivery and converting it into grams per milliliter. It is done by dividing difference in weight of drapes along with sanitary pads with density of blood (i.e 1gm/ml)(7).Estimated total blood loss was calculated by adding the 2 values. If intravenous oxytocin infusion was used during the second stage of labour, it was stopped immediately after delivery. The drape was removed 10 minutes after the episiotomy or laceration repair unless the patient continued to have significant PPH. Patients were further monitored for 1 hours postpartum for PPH and side effects of drugs.

III. Data Analysis and Statistical Analysis

The data collected were entered daily in the master chart. Pre-test of data was done after completing 10 cases and necessary adjustment were made after discussing with the guide. Regular meetings with guide were held to clear up any confusion. Analysis of the data was done. Data were summarized as mean and proportion with the help of the statistician and the final analysis was done using independent t test to test the difference between the 2 different groups. Paired data were analyzed using paired t test. Chi-square test was used to analyze the difference in proportions, and p values were reported accordingly. These findings were then presented in the form of tables, graphs and diagrams. P value was considered significant if $p < 0.05$. SPSS version 21 was the software used for calculation and tabulation of data.

IV. Result

The study population included 300 obstetric cases fulfilling inclusion and exclusion criteria. Out of which 150 received Intramuscular oxytocin 10 units and 150 cases received Intramuscular Carboprost 125μg just after the delivery. The age group ranged between 15-42 years. The mean age group of oxytocin group was 22.85±3.34 years and that of carboprost group was 25.29±4.07 years.101 and 131 women belongs to age group 21-35 years among oxytocin and carboprost groups respectively.

Duration of third stage of labour in oxytocin group ranges from 4-12 minutes and mean duration was 5.57±1.20454. In Carboprost group, the duration ranges from 4-11 minutes with mean duration of 4.85±0.84 .The difference in mean duration of third stage between two groups was 0.72. Intergroup comparison of both study groups showed p value of <0.001 which is statistically significant.

There was reduction of hemoglobin in both the groups. In oxytocin group difference in hemoglobin was 1.49 gm/dl while in carboprost group was 0.78gm/dl.

Comparison of Blood Loss in Study Groups

Blood loss range(ml)	Oxytocin n(%)	Carboprost n(%)
<100	0(0.00%)	41(27.33%)
101-150	0(0.00%)	31(20.66%)
151-200	29(19.33%)	53(35.33%)
201-250	37(24.66%)	18(12%)
251-300	49(32.66%)	2(1.33%)
301-350	31(20.66%)	2(1.33%)
351-400	2(1.33%)	0(0.00%)
401-500	0(0.00%)	1(0.66%)
>500	2(1.33%)	2(1.33%)

The above table shows distribution of both the groups according to amount of blood loss. The postpartum blood loss was less in carboprost group compared to oxytocin group which was statistically significant (p value<0.001) and 2 cases went into PPH in Both groups.

Comparison of Estimated Total Blood Loss

Groups	Total Blood Loss(ml)	
Oxytocin	269±61.83	P<0.001
Carboprost	156±80.01	

The above table shows comparison of blood loss between two groups. The blood loss in Oxytocin group was 269±61.83 compared to carboprost group which was 156±80.01 with p value of 0. 001. Intergroup comparison showed that the mean difference in estimated total blood loss between study groups was 113 with p value of 0.001 which was statistically significant.

In oxytocin group 26 0ut of 150 i.e. 17.3% required additional uterotonics whereas in carboprost group 9 out of 150 i.e. 6.0% required additional uterotonics. The difference in usage of additional uterotonics was statistically significant (p=0.002).

Women in oxytocin group had side effects like nausea and vomiting (6%), shivering (3.33%) and retained placenta (0.66%) while carboprost group had side effects like nausea and vomiting (7.3%), diarrhea (12%) and retained placenta (1.33%).

V. Discussion

This study was conducted in department of obstetrics and gynecology, at National medical college and teaching hospital to evaluate the two uterotonics for management of third stage of labor. 300 women were selected who fulfilled the selection criteria and they were divided in group A and group B 150 of each by computer generated random numbers. In this study we evaluated the efficacy of oxytocin 10 units (group A) with Carboprost 125μg (group B) in the third stage of labour and also recorded duration and blood loss in third stage of labour along with side effects and need for additional uterotonics.

Postpartum hemorrhage has been considered one of the most dreadful cause of maternal mortality worldwide with uterine atony being most common cause (70-90%). Active management of third stage of labour and prophylactic use of oxytocics after the delivery of baby has reduced its incidence by 40% (8,9). Main aim is to prevent PPH.

While it is clear that the use of prophylactic uterotonics will substantially reduce PPH , the most cost effective and ideal uterotonics has not been found, although intramuscular oxytocin is recommended by WHO .Methyl ergometrine is a conventional oxytocics used extensively but with hypertension as side effect. Intramuscular oxytocin has been found effective in preventing PPH even when used alone with fewer side effects. Oxytocin is probably the most commonly used oxytocic but is not the most potent drug and additional dosage or additional drugs may be needed at times with more blood loss compared to other oxytocics(10).

Carboprost is a strong uterotonic agent with a physiological role in human parturition both in the delivery and control of PPH. The discovery of prostaglandins and its analogues as an oxytocics has improved prospect in modern era in control of PPH due to its significant influence on uterine tone resulting in less blood loss that outweighs its cost. The side effects are also subtle(11,12).

VI. Conclusion

In our conclusion, our study favors that intramuscular carboprost 125μg is a better and cost-effective option compared to intramuscular oxytocin 10U and more effective in AMTSL. Carboprost minimized blood loss significantly with less need for additional uterotonics and effectively shortened the duration of third stage of labor compared to oxytocin. The result of our study demonstrated that prophylactic dose of carboprost is well tolerated and may be considered in all woman at risk of PPH. However, a large multicentric randomized controlled trial is required to draw conclusion.

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Maternal and Perinatal Outcomes in Twins conceived Spontaneously Versus by Art – A Prospective Observational Study

By Dr. P. Siva Ranjani Priya, Dr. Maimoona Ahmed & Dr. Prathiba Reddy. T

Abstract- *Background:* Multifetal pregnancies are on the rise due to advanced treatment modalities for infertility and assisted reproductive techniques (ART). These pregnancies are associated with more maternal and fetal morbidities as compared to singleton gestations. Even among twin pregnancies, those conceived by ART have been shown to be associated with adverse outcomes as compared to their spontaneously conceived counterparts.

Objectives: The primary objective was to examine whether DCDA twin pregnancies conceived after ART were at a higher risk of adverse outcomes as compared to their spontaneously conceived counterparts. The secondary objective was to assess the maternal and fetal complications in the twin pregnancies.

Keywords: *DCDA twin pregnancy, Assisted reproductive techniques, Hypertension, Fetal growth restriction, Prematurity.*

GJMR-E Classification: *NLM: WQ 330*

Strictly as per the compliance and regulations of:

Maternal and Perinatal Outcomes in Twins conceived Spontaneously Versus by Art – A Prospective Observational Study

Dr. P. Siva Ranjani Priya [α], Dr. Maimoona Ahmed [σ] & Dr. Prathiba Reddy. T [ρ]

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Objectives: The primary objective was to examine whether DCDA twin pregnancies conceived after ART were at a higher risk of adverse outcomes as compared to their spontaneously conceived counterparts. The secondary objective was to assess the maternal and fetal complications in the twin pregnancies.

Materials and Methods: A prospective observational study was conducted at a tertiary care center in South India from June 2022 to July 2023.The study included mothers with dichorionic diamniotic (DCDA) twin pregnancies conceived spontaneously and by assisted reproductive techniques (ART) such as OI (ovulation induction), ICSI (intracytoplasmic sperm injection) and IVF (in vitro fertilization).Two groups were compared for the maternal outcomes such as maternal medical comorbidity during pregnancy, mode of delivery, and intrapartum complications such as postpartum hemorrhage. Fetal outcomes such as fetal structural or growth abnormalities, fetal demise, NICU admissions, APGAR score at 5 mins, prematurity and its sequelae were also assessed. Mann Whitney U and Chi square test were used for analysis and P value of <0.05 was taken to be statistically significant.

Results: Of the total 162 women in the study, 54 mothers conceived spontaneously and 108 mothers were in the ART group. Maternal complications like hypertension, gestational diabetes mellitus and neonatal complications like premature birth before 34 weeks, APGAR less than 7 at 5 minutes and fetal anomalies were significantly higher in ART group. Fetal growth restriction was significantly higher in the spontaneously conceived group.

Conclusion: The findings of this study strengthen the evidence of higher overall adverse maternal and neonatal outcomes among DCDA twin pregnancy conceived by ART as compared tothe spontaneous group.

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Keywords: DCDA twin pregnancy, assisted reproductive techniques, hypertension, fetal growth restriction, prematurity.

Synopsis

The findings of this study, strengthen the evidence of higher overall adverse maternal and neonatal outcomes among twin pregnancies conceived after ART versus those that are conceived spontaneously.

I. Introduction

In the present era of exponential industrialization and global changes in lifestyle, infertility cases are on an increasing trend. Assisted reproductive technology has become a widespread choice for the treatment of infertility in recent decades. Simple assisted reproduction techniques include induction of ovulation, follicular scanning and intrauterine insemination. If multiple cycles fail or if there is a tubal factor, or a male factor etc., the patients are then recommended in vitro fertilization and embryo transfer popularly referred to as IVF- ET[1].

The increased incidence of multifetal pregnancies has been attributed to two mainfactors: 1) Increased maternal a geat conception, when multifetal gestations are more likely to occur naturally and 2) increased use of assisted reproductive technology (ART), which is more likely to result in multifetal gestation[2]. Multifetal pregnancies are associated with increased risk of maternal complications like pre-eclampsia, eclampsia, preterm delivery, cesarean delivery, and postpartum hemorrhage. Also, there is increased incidence of neonatal morbidity and mortality compared to singleton pregnancies[3]. In spontaneously conceived (SC) pregnancies, the incidence of multifetal gestation is about 2%, while it is up to 40%–50% in in vitro fertilization (IVF) conceived pregnancies[4].Studies have been done to compare the outcomes between spontaneously conceived twins and those conceived by assisted reproductive techniques (ART). However, many studies are inconclusive and contradictory in their findings. We planned our study to compare the maternal and fetal outcomes among dichorionic-diamniotic (DCDA) twin pregnancies. The primary objective was to examine whether DCDA twin pregnancies conceived

after ART were at a higher risk of adverse outcomes as compared to their spontaneously conceived counterparts. The secondary objective was to assess the maternal and fetal complications in the twin pregnancies.

II. Methodology

a) Study Design

We conducted a prospective observational study at a South Indian tertiary care center from June 2022 to July 2023. The DCDA twin pregnancies that were booked at our center and consented to be a part of the study were recruited using convenient sampling technique. We limited our study to only DCDA twin pregnancies to eliminate the bias of higher morbidities associated with monochorionic twin pregnancies. They were divided into two groups- one that conceived spontaneously and the second that conceived after ART (OI (ovulation induction), ICSI (intracytoplasmic sperm injection) *IVF (in vitro fertilization). We excluded women with higher order multiple pregnancies, twins reduced to singleton, triplets reduced to twins, twins with early vanishing twins, and those conceived after only IUI conception. The study was started after receiving the Institutional Review Board approval (EC Reference No. 11_2022).

b) Sample Size

The sample size was calculated assuming the expected proportion of stillbirth in the non-exposure (Spontaneous) group as 20% and the relative risk of stillbirth in ART (exposure) based on the previous hospital records. The required sample size was calculated using the formula proposed by Kirkwood BR et al. The required sample size as per the formula was 270 where 1:2 ratio applied for non-exposure it will be 90 babies and for exposure it will be 180 babies. To account for a non-participation rate/ loss to follow up rate of about 20%, another 18 and 36 twin babies will be added to the sample size. Hence the final required sample size would be 108 and 216 twin babies in non-exposure and exposure groups respectively. We converted the sample size for twin pregnant mothers, it was 54 and 108 mothers in spontaneous and ART groups respectively.

c) Data Collection and Analysis

Data was collected from the electronic medical records and operative notes in a preset proforma. The same was compiled in excel sheet after completion of the sample size. The primary variable was the composite adverse outcome of any of the major maternal and fetal morbidities. For normally distributed quantitative parameters the mean values were compared between study groups using an independent sample t-test (2 groups).

For non-normally distributed quantitative parameters, medians and Interquartile range (IQR) were compared between study groups using Mann Whitney U test (2 groups). Categorical outcomes were compared between study groups using the Chi-square test.

P value < 0.05 was considered statistically significant. Data was analyzed by using coGuide software version 1.0.

III. Results

Total of 162 dichorionic diamniotic twin pregnancies were included, among which the ART group consisted of 108 (66.67%) pregnancies and the spontaneous group encompassed 54 (33.33%) pregnancies.

a) Demographic Comparison

In our study, 53 (98.15%) participants were aged <35 years in spontaneous conception group and in ART conception group, 87 (80.56%) participants were aged <35 years. 25 (46.3%) participants were primigravida and 29 (53.7 %) were multigravida in spontaneous conception group whereas in ART conception group, 59 (54.63%) were primigravida and 49 (45.37 %) were multigravida. In both the study groups, maximum number of mothers gained weight more than 15 kg. In our study most of them delivered by LSCS i.e., 52 (96.3%) participants in spontaneous conception group and in ART conception group, 104 (96.3 %) delivered by LSCS. Table 1 shows the demographic details of the study population.

Table 1: Demography

	Study Group		Chi square value	P value
	Spontaneous Conception (N=54)	ART Conception (N=108)		
Age (years)				
<=35	53 (98.15%)	87 (80.56%)	9.494	0.002*
>35	1 (1.85%)	21 (19.44%)		
Gravida				
Primi	25 (46.3%)	59 (54.63%)	1.001	0.317*
Multi	29 (53.7%)	49 (45.37%)		
weight gain (Kg) (N=162)				
Upto 5 Kg	2 (3.7%)	10 (9.26%)		0.129*
5-10 Kg	15 (27.78%)	20 (18.52%)		
10-15 Kg	12 (22.22%)	38 (35.19%)		
>15 Kg	25 (46.3%)	40 (37.04%)		
Mode of delivery				
LSCS	52 (96.3%)	104 (96.3%)	0.00	1.000*
Vaginal	2 (3.7%)	4 (3.7%)		

**= Chi square test P value*

b) *Maternal Outcome*

In our study, maternal outcomes like hypertensive disorders (12.96%), gestational diabetes mellitus 47 (43.52 %) and postpartum hemorrhage (12.96 %) were higher in the ART group, whereas intrahepatic cholestasis of pregnancy cases were noted higher in the spontaneous group i.e., in 7.41 % cases. Among the four maternal outcomes, Hypertensive disorders (P value 0.001) and gestational diabetes mellitus (P value 0.016) were statistically significant. Figure 2 shows the comparison of the maternal outcomes in both the groups.

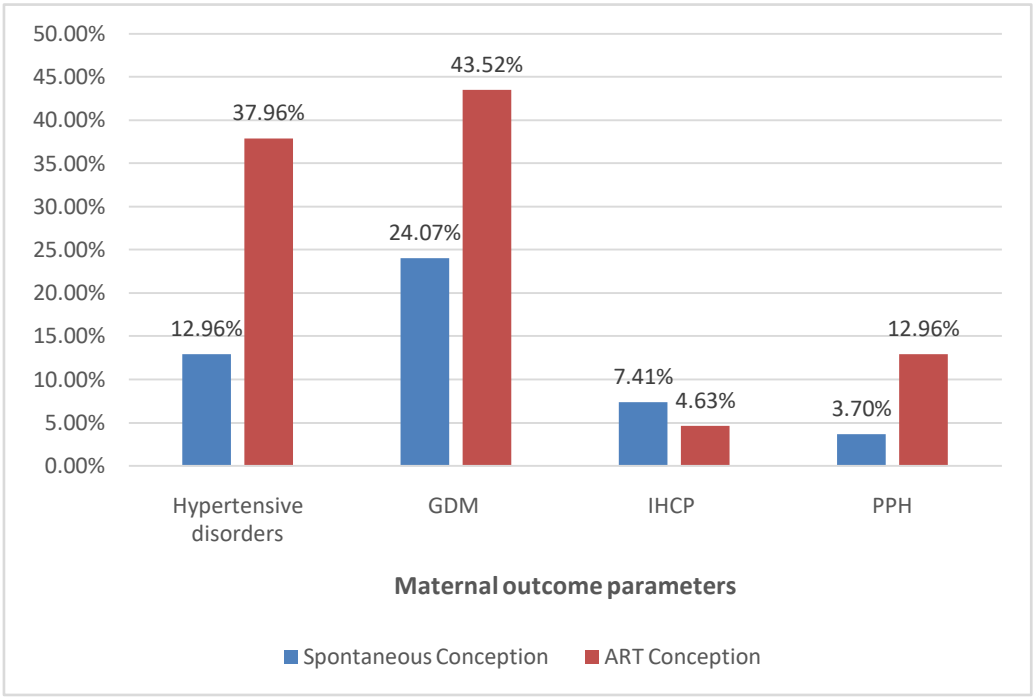

Figure 2: Comparison of Maternal Outcome Parameters with Study Group

c) *Neonatal Outcome*

In spontaneous conception group no babies birthed between 28 to 32 weeks, 12 birthed (11.11%) between 32.1 to 34 weeks, 60(55.56%) between 34.1 to 36.6 weeks and 36 (33.33%) are≥ 37 weeks. In ART conception group, 18(8.33%) babies are between 28 to

32 weeks, 34 (15.74 %) between 32.1 to 34 weeks,110 (50.93%) between 34.1 to 36.6 weeks and 54 (25 %) are ≥ 37 weeks. Figure 3 gives a graphical representation of these results.

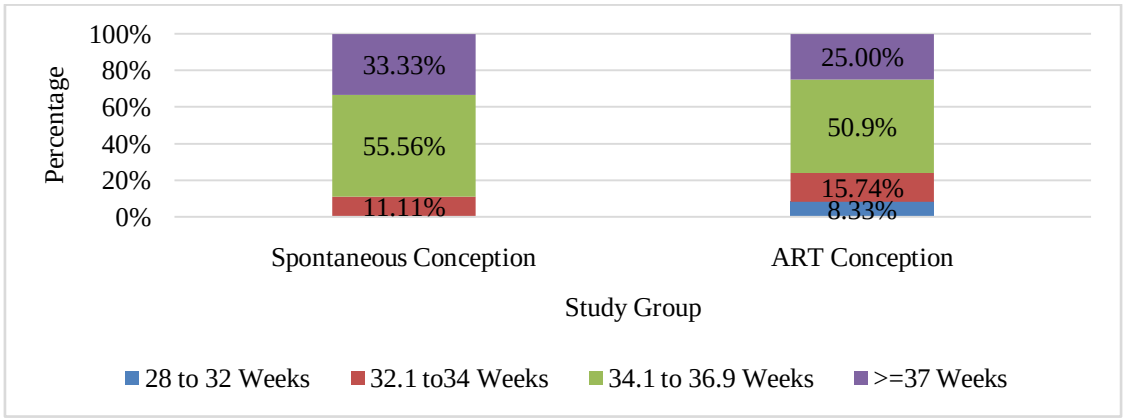

Figure 3: Stacked Bar Chart of Comparison of Preterm with Study Group

In spontaneous conception, APGAR <=7 at 5 minutes of birth seen in 2 (1.85 %) babies and in 15 (6.94 %) babies in ART conception. These are represented in figure 4.

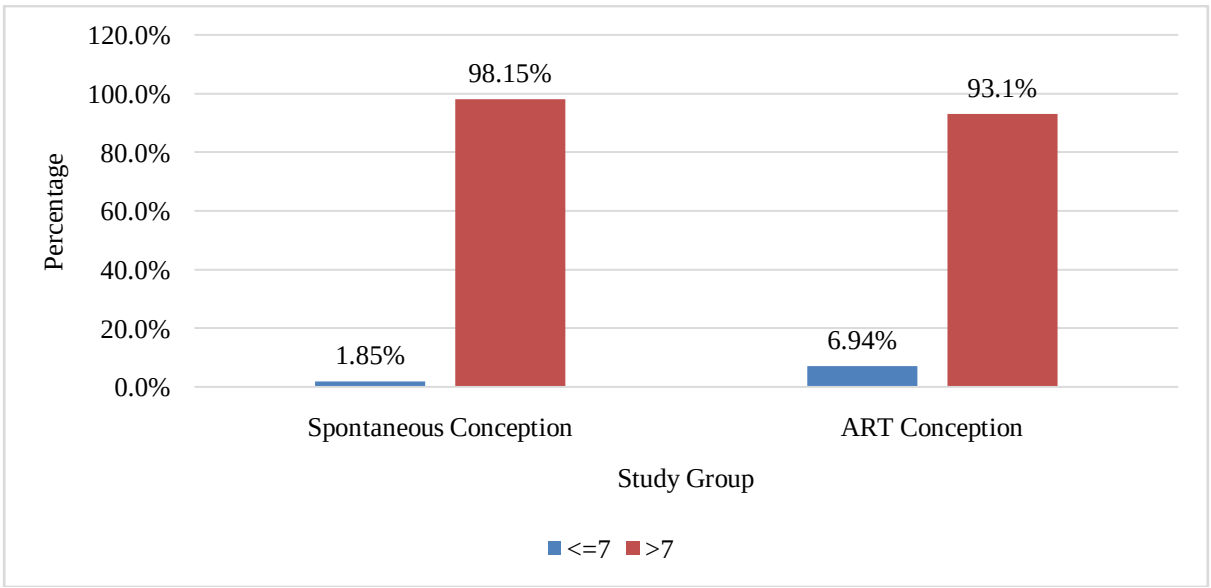

Figure 4: Cluster Bar Chart of Comparison of APGAR at 5 min Between Study Group (N=324)

In the spontaneous conception group, 76 (70.37%) babies were admitted in NICU for more than 48 hours and in ART conception 166 (76.85%) babies admitted.FGR babies were 54 (50%) in spontaneous conception group and 72 (33.33 %) in ART conception group.

3 (2.78%) babies in spontaneous conception group and 19 (8.8 %) in ART conception group had anomalies.

There was no fetal demise in spontaneous conception group, and 4 (1.85 %) fetal demise babies were seen in ART conception group. In spontaneous conception group, no babies had intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP). In ART conception group 2 (0.93 %) babies had IVH and 7 (3.24 %) babies had ROP that required treatment. Figure 5 gives the graphical details of the neonatal outcomes. Of all the neonatal outcomes, Prematurity(P value 0.005), APGAR at 5 mins (P value 0.053),fetal anomalies(P value 0.042),FGR(P value 0.004) were statistically significant.

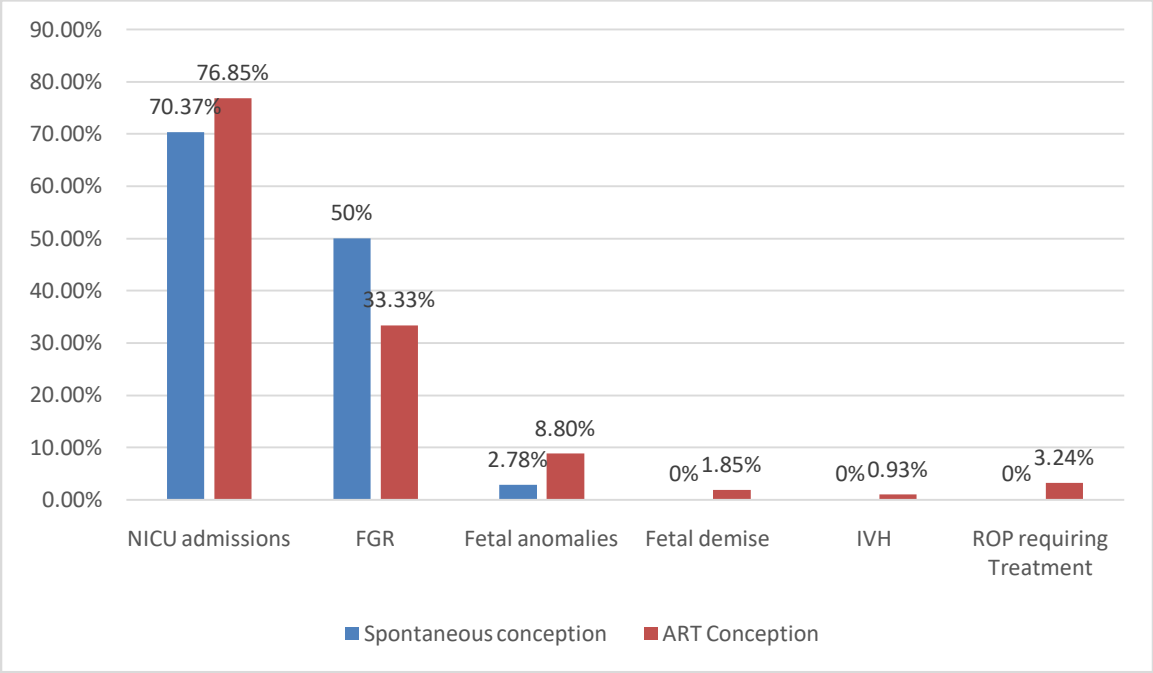

Figure 5: Comparison of Neonatal Outcome Parameters with Study Group

IV. Discussion

The current prospective study included a total of 162 dichorionic diamniotic (DCDA) twin pregnancies, i.e, spontaneous conception group with 54 DCDA twin pregnancies conceived spontaneously and the other group is ART conception group, that included 108 DCDA twin pregnancies conceived by assisted reproductive techniques like ovulation induction, in vitro fertilization, intracytoplasmic sperm injection based on the inclusion criteria and both the groups were compared for the maternal and perinatal outcomes.

Overall, most of the mothers in our study were less than 35 years of age. Older women more than 35 years were more in ART group which is statistically significant (P value <0.002). The studies done by Ching Hong Ho[5] and Preeti Patil et al[1] also noted the same findings in relation to maternal age. The other demographic outcomes like parity, weight gain and mode of delivery were statistically insignificant. Maternal outcomes like Hypertensive disorders and Gestational diabetes were more in the ART group with statistical significance which are in line with the studies done by Diana Rashid et al[6] and Hua Chen et al[4].The other maternal outcomes like IHCP and PPH were statistically insignificant in our analysis.

Our study showed that premature twins were more in the ART group than the spontaneous group and the results were statistically significant (P value 0.005). Similar findings were noted in studies done by Geisler et al[7] and Caserta D et al[8].

The 5 minute APGAR score of less than 7 was found to be more in the ART group which was statistically significant. Study by Ching Hong HO et al[5] showed the prevalence of twins with APGAR less than 7 at 5 minutes was more in spontaneous group (7.4 %) compared to ART group (1.4 %). But other studies such as those done by Leila Pourali et al[9] showed no difference between the two groups in the prevalence of twins with APGAR less than 7 at 5 minutes.

When other neonatal outcomes like NICU admissions for more than 48 hours, fetal demise, intraventricular hemorrhage, retinopathy of prematurity requiring treatment were compared between the 2 groups, they were found to be statistically insignificant. The prevalence of fetal anomalies in our study was overall more in the ART group which was statistically significant. This showed that the twins conceived by ART had a higher risk of structural abnormalities as compared to those that conceived spontaneously.

Diana Rashid et al[6], also concluded the same in their study. In our study the prevalence of fetal growth restriction was more in the spontaneous group (50 %) than ART group (33.33%), which was statistically significant. This was the only fetal morbidity that was found higher among the spontaneously conceived group as compared to the ART group in our study. Studies done by Da Silva et al[10] and Leila Pourali et al[9] have showed the prevalence of fetal growth restriction to be more in the ART group but, there was no statistical difference between the two groups. There were no cases of neonatal and perinatal mortality in our study.

V. Conclusion

The present study concluded that mothers in ART group were older and mostly primigravida. Maternal

complications like hypertension, gestational diabetes mellitus and neonatal complications like premature birth before 34 weeks, APGAR less than 7 at 5 minutes and fetal anomalies were significantly higher in ART group. Our study also concluded that fetal growth restriction was significantly higher in the spontaneously conceived group.

The findings of this study, strengthen the evidence of higher overall adverse maternal and neonatal outcomes among twin pregnancies conceived after ART versus those that are conceived spontaneously.

Author Contributions

Corresponding author - P.SivaRanjani Priya	
	-Data collection, conduct, analysis.
Second author	-Dr. Maimoona Ahmed
	-Planning, analysis, writing.
Third author	-Dr.Prathiba Reddy
	-Planning, design.

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Fellows/Associates of Medical Research Council

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- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
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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)

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g) Suitable statistical data should also be given.
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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 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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