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Original Research Article

Interventions for gestational diabetes: impact of assisted reproduction

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ABSTRACT

Background: This study was to assess whether assisted conception acts as a predictor for insulin therapy in gestational diabetes (GDM) treatment. The secondary aim of this study was to analyse the type of interventions that aided control of blood glucose. The role of ART as a risk factor that increases the risk of insulin therapy in GDM remains elusive. Many studies have established the increased association of GDM with ART conceptions. Factors like advanced maternal age, polycystic ovarian syndrome or obesity that increase GDM risk also contribute to subfertility. Increased level of Hb A1C, elevated FBS values are considered as risk factors for antenatal insulin therapy in women with GDM. This study was to assess if assisted reproduction is an independent variable associated with insulin therapy.

Methods: In this retrospective study, GDM was diagnosed by fasting blood sugar and 2 hours postprandial or 75 gms OGTT based on IADPSG criteria with FBS >90, 2hr >140. Among the 121 GDM mothers, 42 women were ART conceptions and 79 were spontaneous conceptions. The entire study population (121) was divided into 3 groups based on the treatment required. Diet and lifestyle modifications only, diet and life style modifications with OHA and OHA with or without insulin therapy. The demographic, clinical, biochemical data were compared between groups. Details were obtained from case notes and entered in an excel sheet and SSPS software was used for statistical analysis. Inclusion criteria was all GDM pregnancies in the study period (4 years; January 2014 to December 2017) for whom case notes were available. Exclusion criteria was women with diabetes prior to pregnancy, those who moved elsewhere for delivery and multiple gestations.

Results: There was no difference in the insulin requirement between ART conception and spontaneous conceptions. Out of 121 women, 34 women (28%) required diet and life style management, 38 women required OHA (31%), 49 women required insulin (40%). 73% of women who were managed with diet were spontaneous conceptions. Preterm labor was the commonest complication encountered (17%). ART women had more number of perinatal complications, in all treatment groups.

Conclusions: ART was not a predictor for insulin therapy in this study group. The largest group of intervention for GDM was with insulin, 40%. Perinatal complications were seen more in ART mothers with GDM compared with spontaneous conceptions. Spontaneous conceptions women had more percentage of management with diet and life style modifications.

Keywords: ART, GDM, Predictors of insulin

INTRODUCTION

ART is increasingly being practiced and contributes to a significant proportion of deliveries worldwide. There is

an increased risk of GDM for assisted conceptions compared with normal conception.¹ High prevalence of GDM has been reported to range from 3.8% to 17.9% in India.² The geographical differences in prevalence has

been observed. This could be due to differences in age, socioeconomic status of pregnant women and the type of population (tertiary hospital versus community) in various studies.

Nearly 4 million women have GDM in India, at a given time.³ Screening and appropriate management of diabetes during pregnancy provides a unique opportunity to prevent pregnancy complications and limit long term effects by continued screening.

This study was to check the hypothesis if ART increases the risk of insulin therapy in women with GDM. We examined the predictive potential of other clinical and biochemical parameters for insulin therapy. This study was to assess whether ART conception acts as a predictor for insulin therapy to control blood glucose levels. The secondary aim of this study was to analyse the type of interventions that aided control of blood glucose.

METHODS

The present research is a retrospective study that included 140 Indian pregnant women with GDM over a 4 year study period of January 2014 to December 2017. The ART group included singleton pregnancies conceived following ICSI cycles. The protocol of infertility treatment was individualized as per current standard international guidelines.⁴

The diagnosis of GDM in our institution was made by measuring FBS and 2 hours postprandial or 75 g OGTT. The test was done at booking, 20-24 weeks and at 30-34 weeks. FBS more than 90 mg/dl and a 2 hours post glucose value of 140 mg/dl were taken as GDM. Inclusion criteria was all GDM pregnancies in the study period for whom case notes were available. The exclusion criteria was preexisting diabetes, multiple pregnancy and patients who were lost to follow up. Medical records were searched for clinical and demographic data. Pre pregnancy BMI was calculated according to standard formula (kg/m^2).

All GDM women were provided diet advice and advised walking as an exercise for 30-40 minutes each day as exercise. FBS, 2 hour pp blood glucose was rechecked after 2 weeks initially. Subsequent frequency of blood glucose testing was at the least once in 2-3 weeks when values showed good control; FBS was <95 mg/dl and PPBS <126 mg/dl. More frequent individualized glucometer testing along with diabetologist follow-up was arranged when the initial blood glucose values were significantly elevated or remained uncontrolled with lifestyle changes. Oral hypoglycaemic agents was initiated by obstetricians or diabetologist when despite lifestyle modifications, FBS/PPBS values were above target levels. Subcutaneous injections of rapid acting and or long acting insulin was prescribed according to blood glucose patterns by diabetologist.

RESULTS

In this study, 42 women were conceived with ART and 79 were spontaneous conceptions (Figure 1). ART and spontaneous conception groups were comparable for age and parity (Table 1). 28% were managed with lifestyle modifications, 31% were managed with OHA and 40% were managed with insulin (Figure 2). The requirement of insulin was similar in both spontaneous and ART conception groups (Table 2). Women on insulin in both groups had similar perinatal outcomes to the other groups.

Higher proportion of ART women (40% versus 58%) had diagnosis of GDM before 24 weeks, but was not statistically significant. 15 women were diagnosed before 10 weeks of gestation. 10 women were identified after 34 weeks of gestation, by elevated blood glucose levels, following ultrasound findings for large for dates or polyhydramnios (Table 4).

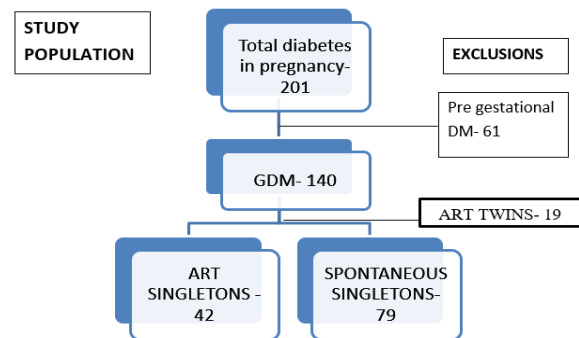


Figure 1: Study population.

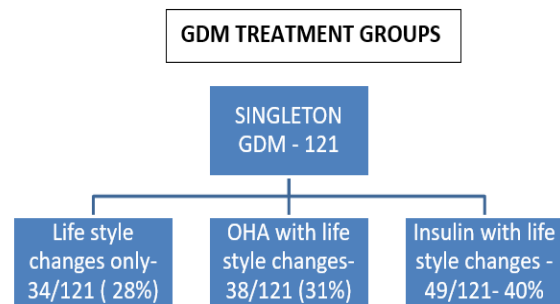


Figure 2: GDM treatment groups.

Comparing the perinatal outcomes, ART conception group had more incidence of perinatal complications (Table 5). Significant correlation in the occurrence of antenatal complications could be seen in ART conception women. Out of all the complications, preterm labour was the commonest (17%). Among the women with antenatal complications, significantly higher complications occurred in women in ART group managed with OHA. (Table 6).

Table 1: Comparison of maternal age, parity with type of conception (N=121).

Parameters	Conception method		P value
	Spontaneous (N=79) (%)	Art conception (N=42) (%)	
Age (in years)			
≤25	5 (6.33)	1 (2.38)	0.816
26-30	32 (40.51)	19 (45.24)	
31-35	32 (40.51)	15 (35.71)	
36-40	9 (11.39)	6 (14.29)	
>40	1 (1.27)	1 (2.38)	
Parity			
Primi	32 (40.51)	20 (47.62)	0.452
Multi	47 (59.49)	22 (52.38)	

Table 2: Comparison of GDM management with conception method (N=121).

Management	Conception method		P value
	Spontaneous (N=79) (%)	Art conception (N=42) (%)	
Lifestyle modifications	25 (31.65)	9 (21.43)	0.234
OHA	25 (31.65)	13 (30.95)	0.938
Insulin	29 (36.71)	20 (47.62)	0.244

Table 3: Demographics for insulin group (N=49).

Parameters	Conception method		P value	Range (N=49)	
	Spontaneous (N=29)	ART conception (N=20)		Minimum	Maximum
Age (mean±SD)	30.69±3.71	30.9±3.8	0.848	25	38
Gestational age at diagnosis (mean±SD)	26.14±7.4	25.15±8.49	0.667	7	37
Gestation at delivery (mean±SD)	38±1.16	38.1±0.97	0.754	36	40
Baby weight (mean±SD)	3.18±0.5	3.24±0.56	0.692	1.4	4.1
Antenatal complications	10 (34.48%)	6 (30%)	0.742		
Postnatal complications	3 (10.34%)	5 (25%)	0.245		
BMI >30	14 (50%)	14 (50%)	0.5		

Table 4: Comparison of patient demographics with conception method (N=121).

Parameters	Mode of conception		Mean difference	95% CI		P value
	Spontaneous (N=79)	Art conception (N= 42)		Lower	Upper	
Age (in years) (mean±SD)	31±4	32±4	0.83	-0.72	2.38	0.292
Gestational age at diagnosis (weeks) (mean±SD)	26±7	23±8	2.50	-0.37	5.36	0.087
Gestation at delivery (weeks) (mean±SD)	38±2	38±2	0.36	-0.31	1.03	0.285
Baby weight (in kgs) (mean± SD)	3±1	3±1	0.00	-0.22	0.22	0.998

Table 5: Comparison of antenatal and postnatal complications with conception method.

	Spontaneous (%)	ART (%)	P value
Antenatal complications	21 (26.5)	18 (42.8)	0.02
Gestational hypertension	6 (7.5)	4 (9.52)	
Abruption	1 (1.2)	1 (2.3)	
Preterm	13 (16.45)	8 (19.04)	
Macrosomia	4 (5)	4 (9.5)	
IUGR	5 (6.39)	3 (7.1)	
Post-natal complications	18 (22.78)	12 (28.57)	0.483

Table 6: Comparison of management between conception method among antenatal complications (N=39).

Management	Conception method		P value
	Spontaneous (N=21) (%)	Art conception (N=18) (%)	
Lifestyle modifications	7 (33)	5 (27)	0.486
Insulin	8 (38)	6 (33)	0.708
OHA	6 (28.5)	7 (39)	0.02

DISCUSSION

GDM is one of the common major complications in pregnancy in India. Early identification can prevent the neonatal and perinatal complications. The incidence of infertility is found to be 10-15% of the population worldwide. The need for ART methods for conception is increasing worldwide.

Worldwide, the incidence of GDM in ART population is higher than spontaneous conceptions. In earlier studies in our institution, the incidence of GDM in spontaneous conception was 7.9%, but the incidence of GDM in ART conception was 14.9%, which is similar to the study published by Wang et al 2013 that showed a 28% increased incidence of diabetes in ART conceptions.¹

The higher prevalent GDM among ART mothers may have been related to the underlying infertility, such as ovulatory discord or unknown infertility in some cases.⁵ A high insulin resistance was found among patients with PCOS related to hyperandrogenism.⁶ In our study 9 women had PCOS, but equal numbers were present in both spontaneous conception and ART group. This can be due to small study population as a limitation in this study

The change in hormone levels, including estrogen, progesterone and insulin growth factor during ovarian stimulation in ART treatment is a likely factor for increased likelihood of GDM among ART mothers.⁶ The impact of ovarian stimulation was demonstrated by a higher fasting glucose level in the first trimester following IVF conception, with no significant difference in second and third trimester blood glucose for

spontaneous and assisted conceptions.⁵ Exogenous progesterone during pregnancy especially in first trimester for assisted conception can also contribute to first trimester GDM.

For insulin requirement in ART pregnancies, many theories and pathogenesis have been put forward by many research papers so far. The mechanism underlying ART-induced insulin resistance and insulin requirement is partially understood. We assessed the impact of some aspects of ART properties on antenatal insulin requirement and observed no significant correlation. Several hypotheses may be proposed in this regard. First, ART-induced endothelial dysfunction and arterial hypertension, glucose intolerance and insulin resistance.⁸ Second, some ART characteristics may be in charge of insulin resistance and the need for insulin therapy, such as PCOS, the number of embryo transfer and administration of GnRH agonist.⁹ Third, exogenous progesterone during luteal phase and first trimester could be associated with GDM and insulin resistance. Nunes et al 2014 found that progesterone particularly at pharmacological doses increased the generation of reactive oxygen species (ROS) and it could be toxic to pancreatic β -cells as a result of oxidative stress.¹⁰

Wada et al 2010 showed the molecular mechanisms of progesterone involved in the pathogenesis of insulin resistance during pregnancy.¹¹ Progesterone could lead to insulin resistance by the inhibition of GLUT-4 translocation, a decrease in the uptake of glucose by adipocytes and decreased expression of the insulin receptor substrate-1 (IRS-1). The degradation of IRS-1 is one of the primary mechanisms that could cause insulin resistance when exposed to pro-inflammatory cytokines.

In spite of so many theories causing insulin resistance in ART, conclusive studies are lacking to say ART can be taken as a predictor for insulin requirement.

Kouhkan et al 2019 showed the probable association between ART and insulin requirement.¹² But our study failed to show the association. Requirement of insulin was similar between both spontaneous conception and ART groups. WINGS study which shows that with proper MNT and with proper guidance and motivation of antenatal women, insulin requirement can be reduced.³

Barens et al 2016 indicated a prediction model for insulin therapy in GDM women with seven significant independent prognostic factors have been introduced, namely maternal age >30 years, pre-gravid obesity (BMI ≥ 30 kg/m²), prior history of GDM, FBS ≥ 5.3 mmol/l, HbA1c $\geq 5.5\%$ at the initial diagnosis of GDM, early diagnosis of GDM (<24 weeks of gestation) and family history of diabetes.¹³ They concluded that 85.7-93.1% of women had six to seven prognostic factors mentioned above, but 9.3-14% of women had no or one prognostic factor. They also concluded that none of these factors can be taken as individual predictors of insulin requirement. In this study only 5% of ART pregnancies had 6-7 of the above mentioned prognostic factors. Hence these factors were not helpful in prognostication.

CONCLUSION

This study compared the requirement of insulin in ART and spontaneous conceptions in south indian population failed to find an association. Insulin requirement was similar in both ART and spontaneous conception groups. Higher proportion of ART women were diagnosed with GDM before 24 weeks. Antenatal complication rate was higher in the GDM ART pregnancies. Hence further studies with larger study population is required to further confirm the findings.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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