

Original Article

Clinical outcomes of test-tube versus naturally-conceived twins

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Abstract: Objective: To investigate the maternal and neonatal outcomes of test-tube twins and naturally-conceived ones and to make a comparative analysis. Methods: Between January 2013 and December 2016, a total of 1200 women with twin pregnancy and a gestational age ≥ 28 weeks who had received regular follow-up and delivery in the Department of Obstetrics of the Tianjin Central Hospital of Gynecology Obstetrics were recruited in this study. Among them, 850 women with test-tube twins were assigned to the test-tube baby group, and 350 women with naturally-conceived twins were assigned to the natural conception group. The women in the two groups were compared in age, gestational complications, delivery modes, neonatal birth weight, birth defects and perinatal outcomes, and then statistical analyses were conducted. Results: The mean age of pregnant women in the test-tube baby group was significantly older than that of those in the natural conception group ($P < 0.001$); the rates of pregnancy-induced hypertension (PIH) and pregnancy-induced diabetes mellitus (PIDM) in pregnant women were considerably higher in the test-tube baby group than in the natural conception (Both $P < 0.05$); however, the women in the two groups were generally similar in the rates of gestational complications including placenta previa, premature rupture of membranes, intrahepatic cholestasis, premature delivery, and twin transfusion syndromes, as well as birth weight, the incidence of birth defects and the morbidity of perinatal diseases in neonates (All $P > 0.05$). Conclusion: The clinical outcomes of test-tube twins and naturally-conceived ones are basically similar, but close attention should be paid to the maternal blood pressure and glucose levels of the test-tube twins.

Keywords: Natural conception, test-tube baby, twin, neonatal outcome, gestational complications

Introduction

In recent years, the incidence of infertility is on the increase in China. It is reported that the rate of infertility is high up to 10% [1]. With the advances of assisted reproductive technologies, increasing infertile women are conceived by the technology of in vitro fertilization (IVF)-embryo transfer, and the rate of test-tube twin conception is higher than that of natural twin conception [2, 3]. However, whether there are differences in the pregnancy outcomes between test-tube twins and naturally-conceived ones is controversial. Jie et al. held that the maternal and neonatal outcomes of the test-tube babies were worse than those of the naturally-conceived ones [4]. Conversely, Vasario et al. argued that the maternal and neonatal outcomes of test-tube babies and naturally-conceived ones were largely similar [5]. Therefore,

in this study, we included 850 test-tube twin pregnancies and 350 naturally-conceived twin pregnancies in the analysis and compared the clinical outcomes of test-tube twins and naturally-conceived ones, with an aim to lay experimental basis for better guidance of the management of test-tube conception and for health care of perinatal mothers and newborns.

Material and methods

Participants

From January 2013 to December 2016, 1200 women with twin pregnancy and a gestational age ≥ 28 weeks who had received regular follow-ups and delivery in the Department of Obstetrics of the Tianjin Central Hospital of Gynecology Obstetrics were enrolled in this study. Among them, 850 women with test-tube

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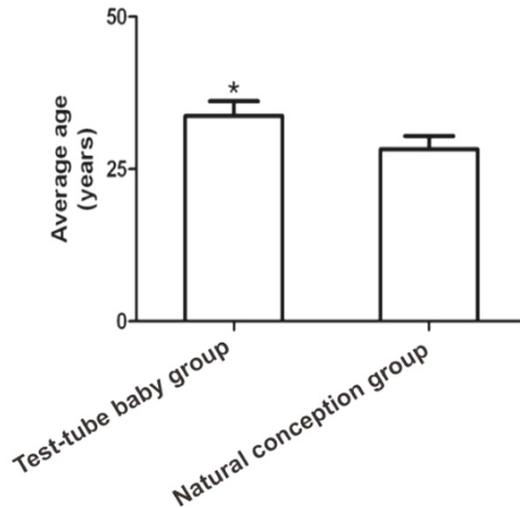


Figure 1. Comparison of age of pregnant women between the test tube baby group and the natural conception group. Compared with the natural conception group, * $P < 0.001$.

twins were assigned to the test-tube baby group, while 350 women with natural-conceived twins were assigned to the natural conception group. Pregnant women were eligible for enrollment if they were primiparas, healthy without any underlying disease, such as diabetes mellitus, hypertension, endocrine disease, or cardiovascular and cerebrovascular disease before pregnancy. Pregnant women were excluded from this study if they had received ovulation stimulation, artificial insemination, application of donated sperm, or in vitro culture of immature ovarian follicles. This study obtained approval from the hospital ethics committee, and all the participants supplied us with written informed consent.

Methods

The clinical data of enrolled pregnant women were collected and a retrospective analysis was conducted. Age and gestational complications of pregnant women were compared between the two groups. Gestational complications included pregnancy-induced hypertension (PIH), pregnancy-induced diabetes mellitus (PIDM), placenta previa, premature rupture of membranes, intrahepatic cholestasis, premature delivery, and twin transfusion syndrome. The ratios of women with vaginal delivery and those with cesarean delivery, neonatal birth weight, and the rates of neonatal birth

defects were also compared between the two groups. Neonatal birth defects covered congenital heart malformation, polydactyly, digestive malformation, cleft palate, hypospadias and neurological abnormalities. Perinatal morbidity was also compared between the two groups. Perinatal diseases included respiratory distress syndrome, intracranial hemorrhage, gastrointestinal bleeding, hyperbilirubinemia, infection and hypoglycemia.

Statistical analysis

The statistical data were analyzed with the use of the SPSS software, version 21.0. Measurement data were described as mean \pm SD and the independent t-tests were employed for between-group comparisons. Count data were expressed as percentages, and the chi-square tests were employed for comparisons between groups. $P < 0.05$ was deemed as statistically significant.

Results

Age of pregnant women

The pregnant women in the test tube baby group were substantially older than those in the natural conception group (33.75 ± 2.41 years vs 28.26 ± 2.18 years; $P < 0.001$), as seen in **Figure 1**.

Gestational complications

The rates of PIH and PIDM were remarkably higher in the test tube baby group than in the natural conception group (Both $P < 0.05$). In contrast, the rates of placenta previa, premature rupture of membranes, intrahepatic cholestasis, premature delivery, and twin transfusion syndrome were insignificantly different between the two study groups (All $P > 0.05$, **Table 1**).

Delivery modes of pregnant women

Among 850 pregnant women in the test-tube baby group, cesarean delivery was reported in 172 pregnant women and vaginal delivery in 678; cesarean delivery was reported in 65 of 350 pregnant women in the natural conception group, and vaginal delivery in 285. The ratios of delivery modes were mildly different between the two groups ($\chi^2 = 0.433$, $P = 0.511$; **Figure 2**).

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Table 1. Gestational complications of the pregnant women (n, %)

Variable	Case	PIH	PIDM	PP	PRM	IC	PD	TTS
TTBG	850	263 (30.94)	237 (27.88)	93 (10.94)	18 (2.12)	72 (8.47)	120 (14.11)	35 (4.11)
NCG	350	67 (19.14)	53 (15.14)	32 (9.14)	6 (1.71)	25 (7.14)	43 (12.29)	11 (3.14)
χ^2		17.309	21.955	0.859	0.206	0.588	0.709	0.639
P		0.001	<.001	0.354	0.650	0.443	0.400	0.424

Note: PIH denotes pregnancy-induced hypertension, PIDM pregnancy-induced diabetes mellitus, PP placenta previa, PRM premature rupture of membranes, IC intrahepatic cholestasis, PD premature delivery, and TTS twin transfusion syndrome, TTBG test tube baby group, NCG natural conception group.

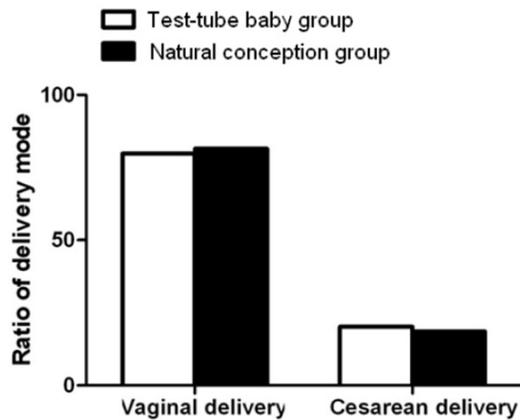


Figure 2. Delivery modes of pregnant women.

Neonatal birth weight

The birth weight of the newborns was 2364.48 \pm 410.67 g in the test-tube group, and 371.39 \pm 427.54 g in the natural pregnant group; the two groups differed insignificant in neonatal birth weight ($P=0.685$).

Neonatal birth defects

The rates of neonatal birth defects including congenital heart malformation, polydactyly, digestive malformation, cleft palate, hypospadias and neurological abnormalities were basically similar between the two groups (All $P>0.05$; **Table 2**), as were the rates of overall neonatal birth defects (20.35% vs 18%, $\chi^2=0.869$, $P=0.351$).

Perinatal diseases of newborns

There were only small disparities in the rates of respiratory distress syndrome, intracranial hemorrhage, gastrointestinal bleeding, hyperbilirubinemia, infection and hypoglycemia of newborns between the two groups (All $P>0.05$). Likewise, the rates of overall perinatal diseases

were largely similar between the two groups (64.71% vs 64.29%, $\chi^2=0.019$, $P=0.890$; **Table 3**).

Discussion

With the advances of medical science and technology, the clinical application of assisted reproductive technologies is a good solution to the problem of infertility in patients [6, 7]. According to the international literature, test tube babies account for nearly 1-4% of all newborns [8]. The proportion of multiple pregnancy in test tube babies is significantly higher than that of natural conception; the proportion of twin pregnancy, in particular, was significantly higher [9, 10]. In recent years, with the increase in the number of test tube newborns, the safety of the test-tube newborns has been drawing growing attention from scholars.

In this retrospective analysis, we enrolled 850 test-tube twin pregnancies and 350 naturally-conceived twin pregnancies for the purpose of comparing the differences of clinical outcomes between them. The results of the analysis showed that the pregnant women with test-tube twins were markedly older than those with naturally conceived twins. This might be due to the fact that pregnant women with test-tube twins had to receive infertility diagnosis and treatment, and it took a long time from starting treatment to successful delivery. This result is consistent with that reported by Pinborg et al. [11]. In terms of gestational complications, the rate of PIH, and PIDM of pregnant women in the test-tube baby group were considerably higher than that of women in the natural conception group; however, the rates of other gestational complications were largely similar between the two groups, which is consistent with what reported by Van Beijsterveldt et al [12]. The higher rate of PIH syndrome in the test tube

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Table 2. Neonatal birth defects (n, %)

Variable	Case	CHM	Polydactyly	DM	CP	Hypospadias	NA
TTBG	850	126 (14.82)	18 (2.12)	16 (1.88)	7 (0.82)	6 (0.71)	0 (0)
NCG	350	45 (12.86)	8 (2.29)	5 (1.43)	3 (0.86)	0 (0)	2 (0.57)
χ^2		0.785	0.033	0.297	0.003	4.150	4.937
P		0.376	0.856	0.586	0.954	0.189	0.085

Note: CHM denotes congenital heart malformation, DM digestive malformation, CP cleft palate, NA neurological abnormalities, TTBG test tube baby group, and NCG natural conception group.

Table 3. Perinatal diseases of newborns (n, %)

Variable	Case	RDS	IH	GB	HB	Infection	HG
TTBG	850	160 (18.8)	48 (5.65)	50 (5.88)	101 (11.88)	158 (18.59)	33 (3.88)
NCG	350	58 (16.57)	15 (4.29)	27 (7.71)	50 (14.29)	58 (16.57)	17 (4.86)
χ^2		0.846	0.924	1.386	1.302	0.683	0.590
P		0.358	0.337	0.239	0.254	0.408	0.442

Note: RDS denotes respiratory distress syndrome, IH intracranial hemorrhage, GB gastrointestinal bleeding, HB hyperbilirubinemia, HG hypoglycemia, TTBG test tube baby group, and NCG natural conception group.

group is probably attributed to the fact of the larger proportion of elderly women among the pregnant women with test tube twins (the elderly primipara is a high risk factor for PIH), the application of chorionic gonadotropin, as well as the immune factors in vitro fertilization [13-15]. The higher incidence of PIDM in the test tube baby group might be due to that infertility is an independent risk factor for PIDM, and also to the elevated levels of progesterone, estrogen and insulin-like growth factors in pregnant women with test-tube twins [16]. This is basically similar to the results of the previous studies [17, 18]. Additionally, there were no significant disparities in the delivery modes between the two groups. Although the pregnant women with test-tube twins had older age, higher rates of PIH and PIDM, and a higher risk for vaginal delivery, the majority of them were still willing to adopt vaginal delivery.

As far as the neonatal outcomes are concerned, the reports on the differences in birth weight between test tube babies and naturally-conceived ones remain controversial [19]. The results of the current study revealed that there were only small differences in neonatal birth weight between the two study groups. It is reported that the rate of birth defects (especially congenital heart malformation) in test tube newborns is strikingly higher than that of naturally-conceived ones [20, 21]. The results

of the current study also indicated that the rates of birth defects differed insignificantly between the test tube babies and naturally-conceived ones, which may be related to the B-ultrasound technique. Moreover, the test-tube and naturally-conceived babies were also insignificantly different in neonatal respiratory distress syndrome, intracranial hemorrhage, gastrointestinal bleeding, infection and neonatal hyperbilirubinemia, hypoglycemia and other perinatal diseases, which is generally consistent with that reported by Daniel et al [22].

In conclusion, the rates of PIH and PIDM were remarkably higher in pregnant women with test-tube twins than in those with naturally-conceived ones. Nevertheless, no significant differences were observed in other maternal and neonatal outcomes. Therefore, the medical staff should pay closer attention to the fluctuations of blood pressure and glucose in pregnant women with test-tube babies. There are still some limitations in the current study, such as the small sample size and the lack of long-term follow-ups. More multi-center studies with larger sample size and long-term follow-ups are required to further compare the long-term clinical outcomes between the test-tube twins and naturally-conceived ones, and to confirm whether the various factors concerning the process of IVF result in higher risks for the development of genetic diseases in test-tube babies.

Disclosure of conflict of interest

None.

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