Abstract

Background: Data vary on maternal and perinatal outcomes of twin pregnancies conceived through assisted reproductive technology compared with spontaneous conception.

Aims: This study compared maternal, perinatal and obstetric outcomes of dichorionic twin pregnancies conceived spontaneously with twin pregnancies conceived through assisted reproductive technology.

Methods: This was a cross-sectional study of dichorionic twins delivered at the Maternity Teaching Hospital, Erbil, Kurdistan Region, Iraq from 1 November 2016 to 31 December 2017. Twin pregnancies were classified into two groups: spontaneously conceived (n = 121) and conceived through assisted reproductive technology (n = 79). Maternal and perinatal outcomes were compared between the two groups. The chi-squared test was used to compare categorical variables and the Student t-test to compare means. Logistic regression analysis was used to assess factors associated with admission to the neonatal intensive care unit.

Results: Pregnancy-induced hypertension, gestational diabetes and preterm rupture of membranes were more common in mothers in the assisted reproductive technology group (P < 0.05). Preterm birth, low neonatal birth weight and congenital malformation were also more common in the assisted reproductive technology group (P < 0.001). Gestational age < 33 weeks and conception through assisted reproductive technology were significantly associated with admission to the neonatal intensive care unit for both twins (P < 0.01).
Conclusion: Studies are needed to understand the reasons for the differences in perinatal and maternal outcomes between twin pregnancies conceived spontaneously and through assisted reproductive technology.

Keywords: assisted reproductive techniques, twin pregnancy, perinatal outcomes, maternal outcomes, Iraq

Citation: Rashid DY; Alalaf SK. Maternal and perinatal outcomes in twin pregnancies conceived spontaneously and by assisted reproductive techniques: cross-sectional study. East Mediterr Health J. 2020; 26(x): xxx–xxx. https://doi.org/10.26719/emhj.20.041

Received: 17/07/18; accepted: 22/10/19

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Introduction

Assisted reproductive technology, including induced ovulation, has become a widespread choice for the treatment of human infertility in recent decades. A consequence of assisted reproductive technology has been the progressive rise in the incidence of twin pregnancies (1). Twin pregnancies are associated with an increased risk of maternal and neonatal morbidity and mortality compared with singleton pregnancies (2–4). Different findings have been reported for neonatal and maternal outcomes, and these variations may be a result of differences in the studied populations and/or in the management of twin pregnancy. Furthermore, data are conflicting on pregnancy outcomes for dichorionic twins (each with a separate placenta and amniotic sac) conceived by assisted reproductive technology compared with those naturally conceived. Some research has suggested that perinatal mortality was significantly lower in twin pregnancy from assisted conception compared with spontaneously conceived twin pregnancy (2,3,5). An increase in antenatal complications has been reported for assisted-conception twin pregnancies, but only limited effects on the morbidity and mortality of an individual pregnancy (5). In contrast, other research has shown an increased risk of adverse neonatal outcomes and increased rate of caesarean delivery, especially in twins conceived by assisted reproductive technology, compared with twins conceived spontaneously. However, there were no significant
differences in the incidences of perinatal death or congenital malformations (5–7).

Given these varying findings, we aimed to compare maternal, perinatal and obstetric outcomes in dichorionic twin pregnancies conceived spontaneously and through assisted reproductive technology in Erbil city, Kurdistan region, Iraq.

**Methods**

**Study design and sample**

This was a cross-sectional study of twins born in the Maternity Teaching Hospital, Erbil City, Kurdistan region, Iraq, from 1 November 2016 to 31 December 2017. The Maternity Teaching Hospital is the only public maternity hospital in the city in which women of different backgrounds give birth, making our sample representative (8,9).

**Inclusion and exclusion criteria**

Inclusion criteria were: dichorionic diamniotic twin delivery, gestational age > 24 weeks and birth weight of each twin ≥ 500 g. Exclusion criteria were: intrauterine foetal death, higher-order multiple pregnancies, deliveries complicated by early vanishing foetuses, twin pregnancies reduced to singleton, and triplet pregnancy reduced to twin pregnancy.

**Data collection and study variables**

Twin births were identified in the outpatient clinic when the pregnant women were admitted to the hospital in order to prepare them for caesarean section or to labour ward for natural labour. They were classified into two groups: conceived through assisted reproductive technology (induction of ovulation and assisted reproductive techniques) and conceived spontaneously.

Pregnant women were followed up from the time of admission and up to 40 days postpartum. Maternal information was recorded in a questionnaire designed for the study which included data on: maternal age, parity, pregnancy complications (pregnancy-induced hypertension, preeclampsia, gestational diabetes mellitus, preterm premature rupture of membranes, antepartum haemorrhage and anaemia in pregnancy). During delivery, data on mode of delivery (vaginal or caesarean) were recorded. After delivery, the following data on the newborn twins were recorded: birth weight, Apgar score, congenital abnormalities, respiratory distress syndrome, admission to the neonatal intensive care unit, and survival in the first week of life. Maternal postpartum complications were also recorded including: postpartum haemorrhage, blood transfusion, postpartum anaemia after one week of delivery and deep vein thrombosis.
Gestational age for twin pregnancies from assisted reproductive technology was calculated from the date of embryo transfer. For spontaneous twin pregnancies, gestational age was calculated according to first trimester ultrasound estimations (10).

Pregnancy-induced hypertension was defined as blood pressure > 140/90 mmHg measured on two occasions 4–6 hours apart after 20 weeks gestation without proteinuria (11). Diagnosis of gestational diabetes mellitus was based on the guidelines of the National Institute for Health and Care Excellence (NICE) – fasting plasma glucose ≥ 5.6 mmol/L, or 2-hour plasma glucose ≥ 7.8 mmol/L (12). Antepartum haemorrhage was defined as any uterine bleeding episode after 24 weeks gestation (13). Preterm premature rupture of membranes was defined as rupture of membranes with amniotic fluid without uterine activity (14). Primary or secondary postpartum haemorrhage was defined as the loss of ≥ 500 mL of blood from the genital tract in a 24-hour period for up to 12 weeks of birth (15). Blood transfusion was performed during management of massive antepartum haemorrhage and/or postpartum haemorrhage from blood loss > 1000 mL and/or signs of clinical shock (16). Anaemia in pregnancy was defined as a haemoglobin concentration < 11 g/L in venous blood (17). Postpartum anaemia was defined by haemoglobin < 11 g/L at 1 week postpartum (18). Diagnosis of deep vein thrombosis was based on guidelines of the Royal College of Obstetricians and Gynaecologists – patient presenting with pain, redness and swelling of left leg. Compression ultrasound confirmed the diagnosis (19).

All neonates were evaluated by an expert neonatologist in the week following birth. Perinatal outcomes included (preterm delivery, admission to the neonatal intensive care unit, low birth weight, congenital malformation, respiratory distress syndrome and stillbirth).

Extremely preterm labour was defined as < 28 weeks of gestation, very preterm (28 to < 32 weeks) and late preterm (32 to < 37 weeks) gestation (20). Birth weight was categorized as: extremely low birth weight = ≤ 999 g; very low birth weight = 1000 to 1499 g, low birth weight = 1500 to 2499 g and normal birth weight = ≥ 2500 g (21). The Apgar score was classified as low (0–3), moderately abnormal (4–6) and reassuring (7–10) (22).

Respiratory distress syndrome was defined as the presence of a characteristic radiographic finding and the need for oxygen for 24 hours (23) in new-borns with tachypnoea, nasal flaring, grunting, intercostal or subcostal retractions and cyanosis (24). Neonatal sepsis was defined as the presence of signs and symptoms of infection with or without accompanying bacteraemia in the first week of life that encompasses various systemic infections of the new-born such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections (25).
Care of mothers and babies

Our institutional protocol for the management of high-risk pregnant women in labour includes teamwork and good communication between health care providers, and response to obstetric emergencies in real time to ensure the perinatal and obstetric safety of twin pregnancies in labour. The clinical management of the pregnant women in both groups was provided by a professional obstetrician and certified nurses and midwives. Vaginal delivery and caesarean section were conducted in a well-equipped labour room and operating room. Both groups were followed up and managed during labour by the same team.

Statistical analysis

Data were analysed using SPSS, version 22. The chi-squared test was used to compare proportions between women with spontaneous and assisted reproductive technology pregnancies according to the variables studied. The Fisher exact test was used when the expected count of more than 20% of the cells of the table was < 5. The Student t-test was used to compare means. Variables found significant with the chi-squared test were included in a logistic regression analysis. The Cramér V was calculated to assess the strength of association between categorical variables (effect size). A P-value ≤ 0.05 was considered statistically significant.

Ethical considerations

The Ethics and Scientific Committee of the Kurdistan Board of Medical Specialties approved this study. Written informed consent was obtained from each woman who agreed to participate in the study at the time of the first interview. All participants were assured that their information would be kept confidential and would be used for research purposes only. All interviews were carried out in accordance with the ethical standards of the institutional research committee.

Results

In total, 247 women with twin pregnancies were interviewed and 7 women were excluded – 5 women for not meeting the inclusion criteria and two women declined to participate. Of the women with twin pregnancies who participated in the study, 121 were spontaneous twin pregnancies and 79 resulted from assisted reproductive technology. Table 1 shows the characters of the women according to whether the twin pregnancy was spontaneous or through assisted reproductive technology.

Cramér V (effect size) showed moderately strong and significant association between both pregnancy-induced hypertension ($V = 0.478, P < 0.001$) and gestational diabetes mellitus ($V = 0.478, P < 0.001$).
Cramér V showed a moderately strong association between preterm birth, low birth weight and depressed Apgar scores and both assisted reproductive technology and spontaneous pregnancy (V ranging from 0.304 to 0.500; Table 3). Significant differences were found between the groups for gestational age, birth weight and Apgar score in first and second twins in favour of spontaneous twins (P < 0.001).

A significantly greater proportion of second-born twins had congenital anomalies in the assisted reproductive technology group than in the spontaneous group (P = 0.036), although the strength of the association was weak (V = 0.158). For both first- and second-born twins, there was a moderately strong association with admission to the neonatal intensive care unit in both the assisted reproductive technology group and the spontaneous group (V = 0.312 for first-born and V = 0.305 for second-born, respectively). In addition, a significantly greater proportion of both first- and second-born twins in the assisted reproductive technology group were admitted to the neonatal intensive care unit than in the spontaneous group (P < 0.001; Table 4).

In logistic regression analysis of the factors associated with admission to the neonatal intensive care unit for the first-born twin (Table 5), gestational age < 33 weeks (OR = 95.24, 95 CI: 20.81–435.87) and being in the assisted reproductive technology group compared with the spontaneous group (OR = 4.94, 95% CI: 1.68–14.52) were both statistically significant risks. In logistic regression analysis of the factors associated with admission to the neonatal intensive care unit for the second-born twin (Table 6), gestational age < 33 weeks (OR = 40.35, 95% CI: 12.75–127.70) and being in the assisted reproductive technology group (OR = 4.94, 95% CI: 1.68–14.52) were both statistically significant risks.

Discussion

Assisted reproductive technologies have been widely recommended all over the world as successful and common treatments following the increased rate of infertility (26,27). As a consequence, rates of twin pregnancies are increased in assisted reproductive treatment cycles (28). In our study, the rates of maternal complications, such as pregnancy-induced hypertension, gestational diabetes mellitus and preterm premature rupture of membranes, were significantly higher in the assisted reproductive technology group compared with the spontaneous group. In contrast, for other complication there was no any difference between the two groups. A 2016 study reported that multiple pregnancies after assisted reproductive techniques are the single most likely explanation for the increased rate of gestational
hypertension and preeclampsia in mothers who had undergone assisted reproductive treatment (29). The authors suggested that a policy to minimize twin pregnancies after these techniques may reduce the increased risk of gestational hypertension and preeclampsia (29). Another study also concluded that poor outcomes (preeclampsia, gestational diabetes and preterm labour) were significantly more common in mothers of twins conceived by assisted reproductive techniques (7). The authors advised that couples should be aware of these potential risks before choosing assisted reproductive techniques (7). However, other research concluded that maternal complications, such as preterm premature ruptures of membranes, pregnancy-induced hypertension and gestational diabetes, were not significantly different between women with assisted reproduction versus spontaneous conception (30). Findings also differ on the other maternal complications with assisted reproduction versus spontaneous conception (31,32).

The differences in the maternal outcomes in the literature may be because of differences in sample sizes for both assisted reproductive technique and spontaneous twins groups, the settings where the research was conducted and the methods used for assisted reproductive techniques.

Poor neonatal outcomes were markedly higher in the assisted reproductive technology group than the spontaneous group in our study. This was in agreement with a prospective follow-up study that reported that assisted reproductive technology twin pregnancies were at greater risk of low birth weight, preterm birth, congenital anomalies, neonatal respiratory distress syndrome and perinatal mortality (33). A review of maternal and neonatal records also found that twins conceived with assisted reproductive technologies compared with twins conceived spontaneously: had a lower mean birth weight for both twins; more neonates weighed < 1500 g; more had Apgar scores < 7 at 5 minutes; more were admitted to the intensive care unit; and more second twins died in the neonatal period (34).

Gestational age < 33 weeks in both twins and conception through assisted reproductive technology were significantly associated with admission to the neonatal intensive care unit for both twins in our study. This finding concurs with other research (33) but not with another study that concluded that perinatal and neonatal morbidity, gestational age at delivery and birth weight were not affected by assisted reproductive techniques compared with spontaneous conception (30). Twin pregnancies conceived via assisted reproductive techniques are at greater risk of poorer outcomes than spontaneous twin pregnancies and this may be related to the type of conception and negative maternal characteristics, for example being subfertile and undergoing infertility treatment.

A strength of our study was that it examined pregnancies in a busy hospital with facilities to
manage women with high-risk deliveries, including twin pregnancies. Another strength is that both groups were similarly managed during labour, including both vaginal and caesarean section deliveries. A limitation of our study is that we did not examine the effect of factors such as socioeconomic status, educational level, food intake and lifestyle on the perinatal outcomes of the twin pregnancies. These factors should be examined in future studies, as well as the reasons for the differences in perinatal and maternal outcomes between twin pregnancies conceived spontaneously and through assisted reproductive technology, including the techniques used in assisted reproductive technology.

Our study supports the findings that pregnancies through assisted reproductive techniques have poorer perinatal and maternal outcomes. The reasons for the worse outcomes in comparison to spontaneously conceived twins are not known and warrant further investigation in a multicentre study with a large sample size, using the same design and follow-up including same treatment protocols for assisted reproductive techniques.

Acknowledgements

We thank all the participants and Charles Allan from Edanz Group for editing a draft of this manuscript.

Funding: None.

Competing interests: None declared.

References


