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Late selective termination and the occurrence of placental-related pregnancy complications: A case control study

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ABSTRACT

Introduction: Multiple pregnancies are at increased risk of placental-related complications. The aim of the study was to investigate the prevalence and cumulative incidence of placental-related complications in twin pregnancies undergoing a late selective termination, compared to matched singleton and twin controls.

Methods: A retrospective case-control study of post-selective late termination (≥20 weeks of gestation) singletons performed between 2009 and 2020 at a single tertiary center. Each post-termination pregnancy was matched to 2 singleton and 2 dichorionic twin pregnancies for: mode of conception, maternal age group and parity. The prevalence of composite placental related outcome was determined and compared. Kaplan-Meier curves were constructed, and log rank test was performed to compare the cumulative incidence of placental complications among groups.

Results: Included were 90 post-selective termination pregnancies and 360 matched singletons and twins. These were subdivided according to trimester at procedure: 1) late 2nd trimester (N = 43, 20–27.6 weeks); 2) 3rd trimester (N = 47, ≥28 weeks).

Placental-related complications presented earlier in the 3rd trimester selective termination group compared to singletons (median 35.5 vs median 37.4 weeks of gestation, P = 0.01). The cumulative incidence of placental-related complications in twins and post-selective termination singletons rose significantly earlier compared to singletons (P < 0.0001).

A late 2nd trimester selective termination resulted in a comparable gestational age and cumulative incidence of placental-related complications as singletons.

Discussion: Compared to singletons, the cumulative incidence of placental complications rises significantly earlier in post-third trimester selective termination singleton pregnancies. While a late 2nd trimester selective termination results in a cumulative incidence comparable to singletons.

1. Introduction

Abnormal placentation is considered an important underlying mechanism of various pregnancy complications including intrauterine growth restriction, preeclampsia, pregnancy induced hypertension, stillbirth and placental abruption, collectively termed "The Great Obstetrical Syndromes" [1–5]. The rate of these complications is increased in multiple compared to singleton pregnancies [6–9], placing these pregnancies at increased risk of fetal compromise [10–14]. Additional obstetric complications which are more common in multiple pregnancies include gestational diabetes [15,16] and intrahepatic cholestasis of pregnancy [17–20].

In order to avoid excessive risk of placental-related adverse outcomes, especially stillbirth, labor induction is recommended at a gestational age which offers a reasonable balance between the risk of developing severe placental-related adverse outcomes and newborns' risk of developing complications of prematurity. The ideal gestational age for labor induction is determined, among other considerations, by pregnancy plurality, chorionicity and amnionicity [21–25]. Late selective termination singletons are a special population since a large duration of their pregnancy they are multifetal, with its associated increased placental-related adverse outcomes, whilst after selective termination,

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they continue as singletons, with an allegedly reduced risk of placental-related complications.

To the best of our knowledge, the manifestation of placental-related adverse outcome in singleton pregnancies following late selective termination compared to twins and singletons has not been reported so far. This information is clinically important for the optimal management of these pregnancies, including timing of delivery. The aim of this study was to determine the rate and cumulative incidence of placental-related adverse outcomes of late selective termination singleton pregnancies and to compare to singleton and twin gestations.

2. Methods

2.1. Study population

This was a retrospective case-control study of post-selective termination singletons resulting from a late selective termination (≥20 weeks of gestation) performed between the years 2009–2020 due to major anomaly, clinically significant genetic abnormality or selective intrauterine growth restriction found in the co-twin. Both mono- and dichorionic pregnancies were included in the study. A study flow chart detailing the process of case exclusion and matching of controls is presented in Fig. 1. Included were cases that met the following criteria: 1. selective termination from a twin pregnancy at 20 weeks of gestation and onwards 2. first trimester ultrasound dating and 3. maternal age between 18 and 45. Exclusion criteria were: missing essential clinical data, higher order multiple pregnancies (more than 2 viable fetuses) prior to selective termination, selective termination before 20 weeks of gestation, termination of the whole pregnancy and procedure related pregnancy loss. Each post-termination singleton pregnancy was matched at a 1:2 ratio to 2 singleton and 2 dichorionic twin pregnancies. Participants were matched for established risk factors of placental related complication [2,6,8,26]: mode of conception (spontaneous, controlled ovulation induction and in-vitro fertilization) maternal age groups (25–29, 30–34, 35–39 and 40–44 years of age) and parity categories (0, 1–5 and ≥6). An additional parameter matched for was year of delivery, to ensure similar clinical management. Data were extracted from the maternal and neonatal computerized medical records.

To make data interpretation more accurate, the study group and their corresponding controls were further divided into 2 subgroups according to the gestational age at time of selective termination: 1) late 2nd trimester, between 20 and 27.6 weeks, 2) 3rd trimester, at 28 weeks and over. Comparisons were conducted for the entire cohort and their control groups and also for each subgroup with its corresponding controls. A sub-analysis including post-selective termination singletons of Dichorionic origin and their controls was conducted, additionally.

2.2. Method of selective termination

Dichorionic pregnancies (n = 61) were selectively terminated by intracardiac potassium chloride injection. Monochorionic (n = 29) selective termination was performed by either bipolar cord ligation in 17.24% of cases (5/29) or radiofrequency umbilical cord ablation in 82.76% of cases (24/29).

2.3. Outcome measures

Parameters compared between the study (late-selective termination singletons) and control (twins and singletons) groups included the following: rate and gestational age at detection of composite placental-related adverse outcome (stillbirth, pregnancy induced hypertension, preeclampsia, placental abruption, oligohydramnios and intrauterine growth restriction, as defined below). The median gestational age of composite placental-related adverse outcome was based on the gestational age of the first presenting placental adverse outcome. Gestational diabetes (GDM) and intrahepatic cholestasis of pregnancy (IHCP) were also compared as these are significant conditions and more common in twins, albeit not considered placental-related adverse outcomes.

Composite neonatal adverse outcome compared, included: respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). In addition, the rate of RDS, as a single complication was also determined and compared among groups.

2.4. Definition of conditions

Throughout the period of the study, definitions of conditions might have changed, but the following are as per department protocols.

Stillbirth-fetal demise beyond 20 weeks of gestation.

Pregnancy induced hypertension-new onset of hypertension beyond 20 weeks of gestation (≥140 systolic blood pressure and/or ≥ 90 diastolic blood pressure, on at least 2 occasions at least 4 hours apart) without other pre-eclamptic features (detailed below).

Preeclampsia-new onset of hypertension beyond 20 weeks of gestation (≥140 systolic blood pressure and/or ≥ 90 diastolic blood pressure, on at least 2 occasions at least 4 h apart) accompanied by additional pre-eclamptic features (proteinuria ≥0.3 g in a 24 h urine specimen or ≥2+ on a random dipstick, platelet count <100,000, serum creatinine>1.1

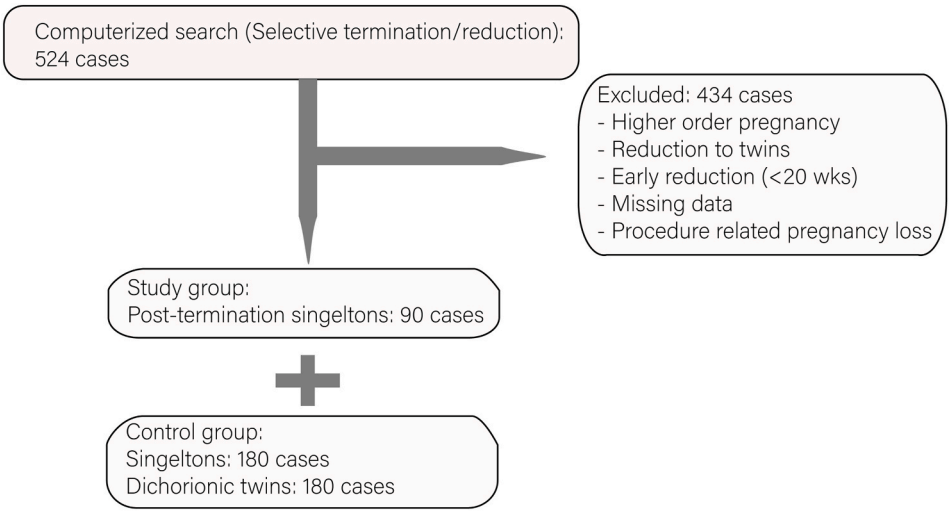


Fig. 1. Study flowchart.

mg/dL, elevated liver transaminases at least twice the upper limit, pulmonary edema, new onset headache not attributed to another diagnosis and not alleviated by analgesics, visual symptoms).

Placental abruption- Overt: abrupt onset of vaginal bleeding and abdominal/back pain, accompanied by uterine contractions, Concealed: abdominal/back pain and uterine contractions with evidence of a retroplacental/retrochorionic hematoma.

Oligohydramnios-amniotic fluid index ≤50 mm in singleton pregnancies, maximal vertical pocket ≤20 mm in twins and singletons.

Intrauterine Growth Restriction-estimated fetal weight below 10th centile.

Gestational Diabetes Mellitus- 2 pathological values on a 100-g oral glucose challenge test or ≥200 mg/dL on a 50-g glucose challenge test.

Intrahepatic Cholestasis of Pregnancy- Characteristic pruritus (predominately on palms and soles, worse at night) accompanied by elevated total bile acid or liver transaminases.

Respiratory Distress Syndrome- Progressive respiratory failure shortly after birth in a preterm neonate, manifested by an increase in work of breathing and in oxygen requirement in conjunction with a characteristic chest radiograph.

Necrotizing Enterocolitis- Abdominal distention, bilious vomiting/gastric aspirate, and rectal bleeding in the absence of an anal fissure in conjunction with intramural gas or pneumoperitoneum on imaging.

Intraventricular Hemorrhage-evidence of bleeding in the germinal matrix or in the lateral ventricles on postnatal head ultrasound.

Bronchopulmonary Dysplasia-requirement of oxygen supplementation either at 28 days postnatal age or 36 weeks postmenstrual age.

Retinopathy of Prematurity-characteristic retinal changes detected on an ophthalmologist exam in a premature neonate, corresponding to the International Classification of Retinopathy of Prematurity [27].

2.5. Statistical analysis

Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Data are presented as percent and numbers or median and inter-quartile range (IQR), as appropriate. Comparison between two unrelated variables was conducted with Student's t-test or Mann–Whitney *U* test, as appropriate. The Chi-Square and Fisher's Exact tests were used for comparison between categorical variables. Comparisons among the three groups were performed using the Kruskal–Wallis test with post hoc test. For those normally distributed parameters parametric tests were used for analysis and the comparisons among groups were performed using one-way ANOVA with Bonferroni adjustment for the calculated p-value in order to maintain the significance level at 0.05.

Kaplan-Meier curves were constructed, and log rank test was performed to compare the cumulative incidence of composite placental outcomes from 20 weeks of gestation until delivery, between the study groups and each of the control groups (singleton and twin pregnancies). A one minus survival plot was chosen to depict the trajectory of cumulative incidence of placental related adverse outcome with advancing gestation.

Significance was determined at $p < 0.05$ and borderline significance at $P = 0.05–0.1$. Statistical analyses were conducted using IBM SPSS v.25(IBM Corporation Inc., Armonk, NY, USA).

The study protocol was approved by the Institutional Ethical Committee (approval number SMC-6073-19).

3. Results

Retrieved were 524 cases of selective termination, of which 434 were excluded due to one or more exclusion criteria (Fig. 1). Three cases were excluded due to procedure related pregnancy losses that occurred between day one and 3-weeks post-procedure. All 3 cases were monochorionic twins and were performed by radiofrequency ablation between 20 and 22 weeks. The study group included 90 pregnancies that met the inclusion criteria. Of these, 43 pregnancies were selectively terminated between 20 and 27.6 weeks (late 2nd trimester group), and 47 cases were performed between 28 and 35 weeks (3rd trimester group). The 2nd trimester group was comprised of 65.1% (28/43) monochorionic twins and the 3rd trimester group were mostly dichorionic twins,97.9% (47/48). There was a similar length of latency period for dichorionoc pregnancies selectively terminated in the 2nd trimester by intra-cardiac KCl injection (n = 15, median 108 days, IQR 91.5–114.5) and monochorionic pregnancies terminated by bipolar ligation or radiofrequency ablation (n = 28, median 103.5 days, IQR 75.5–117.25), $p = 0.57$. A comparison of background demographic data between the study group and their matched control groups is presented in Table 1. There were no statistically significant differences among the groups.

4. Placental-related adverse outcome

4.1. Late selective termination (≥20 weeks)

As a group, post-late selective termination singletons presented a similar rate of placental-related composite adverse outcome as both twins and singletons (30% vs 24.4%, $P = 0.33$, and 30% vs 37.8%, $P = 0.24$) as well as similar rates of GDM (8.9% vs 8.3%, $P = 0.88$, and 8.9% vs 13.3%, $P = 0.29$) and IHCP (1.1% vs 1.1%, $P = 1$ and 1.1% vs 5%, $P = 0.17$) (Table 2). However, the gestational age of composite placental-related adverse outcome presentation was significantly earlier in the study group compared to singletons (median 35.6, IQR 32.6–37, vs median 38.3, IQR 35.5–39.5, weeks of gestation, $P = 0.002$), and similar to that of twins (median 35.6, IQR 32.6–37, vs median 35, IQR 31.4–36.6, weeks of gestation, $P = 0.28$).

Fig. 2 is a Kaplan-Meier curve comparing the cumulative incidence of placental-related adverse outcome of the entire late selective termination group to that of matched twins and singletons. The cumulative incidence of composite placental-related adverse outcomes rose earliest among twins and latest among singletons, with a statistically significant difference between these curves ($P < 0.0001$). The cumulative incidence of composite placental-related adverse outcome of the study group increased significantly earlier than in singletons ($P < 0.0001$), and similar to twins ($P = 0.286$).

4.2. Third trimester selective termination (≥28 weeks)

In analysis of the 3rd trimester selective termination singleton subgroup (Table 3A), there was a borderline significant difference in the rate of composite placental-related adverse outcomes between the study group and the singleton group (40.4% vs. 25.5%, $P = 0.07$). Furthermore, the diagnosis of composite placental-related adverse outcome was significantly earlier in the study group compared to the singleton group (median 35.5, IQR 32.1–36.4, vs median 37.4, IQR 34.6–39.5, weeks of gestation, $P = 0.01$) and similar to twins' group regarding both the rate of placental-related adverse outcomes and gestational age at adverse outcome detection (40.4% vs. 43.6%, $P = 0.72$; median 35.5, IQR 32.1–36.4 vs median 34.1, IQR 30–36.4 weeks of gestation, $P = 0.39$). No statistically significant difference was detected between the study and control groups regarding the rate of both GDM and IHCP.

Fig. 3A is a Kaplan-Meier curve comparing the cumulative incidence of placental-related adverse outcomes between the 3rd trimester selective termination group to that of the twins and singletons groups. The cumulative incidence of composite placental-related adverse outcomes showed a similarly early and sharp incline in both the twins and study groups ($P = 0.99$) in contrast to the delayed and more gradual incline among singletons, with a statistically significant difference between the former 2 curves and latter curve ($P < 0.0001$).

Table 1
Characteristics of study and control groups.

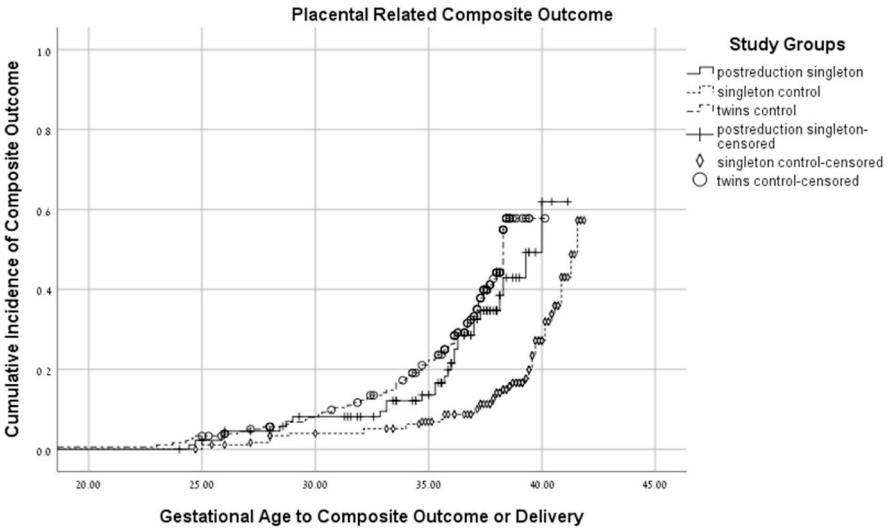
Characteristics		Post-Selective Termination Singletons (N = 90)	Singleton Control Group (N = 180)	P value	Twin Control Group (N = 180)	P* value
Maternal Age (Years)		34 (30–38)	35 (30.2–38)	0.98	35 (30–38)	1
Gravidity		2 (1–3)	2 (1–3)	0.46	2 (1–3)	0.15
Parity		1 (0–2)	1 (0–1)	0.5	1 (0–2)	0.8
Mode of Conception	Spontaneous	53.3% (48/90)	53.3% (96/180)	1	53.3% (96/180)	1
	COH	10% (9/90)	10% (18/180)	1	10% (18/180)	1
	IVF	36.7% (33/90)	36.7% (66/180)	1	36.7% (66/180)	1
BMI (kg/m^2)		22.1 (19.5–25.4)	23.3 (21.2–26.8)	0.1	22.6 (20.6–26.4)	0.3

Data are presented as percentage (n/N) or median (Interquartile Range).
IVF, *in vitro fertilization*; COH, *controlled ovarian hyperstimulation*; BMI, *body mass index*. *Comparison between Selective Termination Singleton Study Group and Twin Control Group.

Table 2
Placental related adverse outcome.

	Post- Selective Termination Singleton (N = 90)	Singleton Control Group (N = 180)	P value	Twin Control Group (N = 180)	P value[a]	P value[b]
Placental related Composite Adverse Outcome	30% (27/90)	24.4% (44/180)	0.33	37.8% (68/180)	0.24	**0.009**
Gestational age at Composite Outcome (weeks)	35.6 (32.6–37)	38.3 (35.5–39.5)	**0.002**	35 (31.4–36.6)	0.28	**<0.0001**
GDM	8.9% (8/90)	8.3% (15/180)	0.88	13.3% (24/180)	0.29	0.13
IHCP	1.1% (1/90)	1.1% (2/180)	1	5% (9/180)	0.17	**0.03**

Data presented as Percentage (n/N) or Median (Interquartile Range).
Placental related composite adverse outcome includes: Intrauterine growth restriction, Preeclampsia, Pregnancy induced hypertension, Oligohydramnios, Placental abruption, Stillbirth.
GDM, *Gestational Diabetes Mellitus*; IHCP, *Intrahepatic Cholestasis of Pregnancy*.
[a] Comparison between Selective Termination Study group and Twin Control group.
[b] Comparison between Singleton and Twin Control groups.



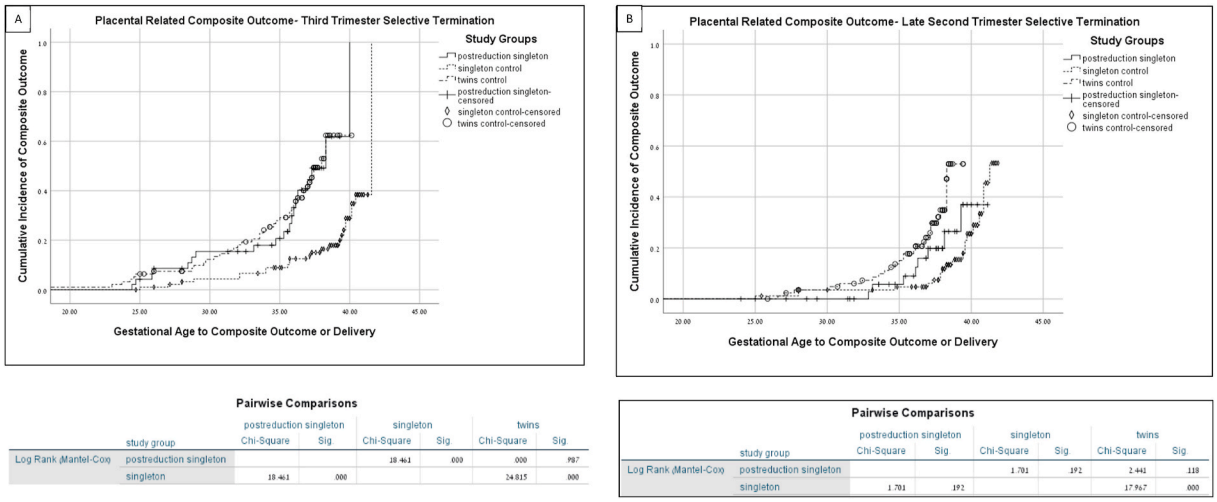
		postreduction singleton		singleton control		twins control	
	study group	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	postreduction singleton			16.958	.000	1.136	.286
	singleton control	16.958	.000			42.851	.000
	twins control	1.136	.286	42.851	.000		

Fig. 2. Comparing the cumulative incidence of placental related composite adverse outcome between post-late selective termination singletons and matched twins and singleton control groups using a One Minus Survival Kaplan Meier curve.

Table 3
Placental related adverse outcome A. Third Trimester Selective Termination Group (>28 weeks of gestation) B. Late 2nd Trimester Selective Termination Group (20–27.6 weeks of gestation).

A	Third Trimester Selective Termination (N = 47)	Singleton Control Group (N = 94)	P value	Twin Control Group (N = 94)	P value[a]	P value[b]
Placental related Composite Adverse Outcome	40.4% (19/47)	25.5% (24/94)	**0.07**	43.6% (41/94)	0.72	0.009
Gestational age at Composite Outcome (weeks)	35.5 (32.1–36.4)	37.4 (34.6–39.5)	**0.01**	34.1 (30.0–36.4)	0.39	0.001
GDM	12.8% (6/47)	9.6% (9/94)	0.56	14.9% (14/94)	0.73	0.27
IHCP	2.1% (1/47)	1.1% (1/94)	1	6.4% (6/94)	0.42	0.12
B	Late 2nd Trimester Selective Termination (N = 43)	Singleton Control Group (N = 86)	P value	Twin Control Group (N = 86)	P value*	P value**
Placental related Composite Adverse Outcome	18.6% (8/43)	23.3% (20/86)	0.55	31.4% (27/86)	0.12	0.3
Gestational age at Composite Outcome (weeks)	36.1 (33.5–37.6)	39.0 (37.3–40.0)	0.2	36 (34–37.2)	0.5	**0.03**
GDM	4.7% (2/43)	7% (6/86)	0.6	11.6% (10/86)	0.2	0.3
IHCP	0%	1.2% (1/86)	1	3.5% (3/86)	0.55	0.62

Data presented as Percentage (n/N) or Median (Interquartile Range).
Placental related composite adverse outcome includes: Intrauterine growth restriction, Preeclampsia, Pregnancy induced hypertension, Oligohydramnios, Placental abruption, Stillbirth.
GDM, *Gestational Diabetes Mellitus*; IHCP, *Intrahepatic Cholestasis of Pregnancy*.
[a] Comparison between Selective Termination Study group and Twin Control group.
[b] Comparison between Singleton and Twin Control group.



Pairwise Comparisons

		postreduction singleton		singleton		twins	
	study group	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	postreduction singleton			18.461	.000	.000	.987
	singleton	18.461	.000			24.815	.000

Pairwise Comparisons

		postreduction singleton		singleton		twins	
	study group	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	postreduction singleton			1.701	.192	2.441	.118
	singleton	1.701	.192			17.967	.000

Fig. 3. One Minus Survival Kaplan Meier curve comparing the cumulative incidence of placental related composite adverse outcome between A) post-3rd trimester selective termination singletons and matched twins and singleton control groups B) post-late 2nd trimester selective termination singletons and matched twins and singleton control groups.

4.3. Dichorionic third trimester selective termination

Table 4A and Fig. 4A display the comparison of the rate, gestational age and cumulative incidence of composite placental-related adverse outcome of post- 3rd trimester selective termination singletons originating from dichorionic pregnancies and their corresponding controls. The results were similar to the third trimester selective termination comparison which included monochorionic originating pregnancies.

4.4. Late 2nd trimester selective termination (20–27.6 weeks)

In the late 2nd trimester selective termination subgroup comparison (Table 3B), the rate of placental-related adverse outcome in the study group was similar to that of singletons (18.6% vs. 23.3%, P = 0.55) and twins (18.6% vs. 31.4%, P = 0.12). Moreover, there were no statistically significant differences in the gestational age at time of adverse outcome detection between the study group (median 36.1 IQR 33.5–37.6 weeks of gestation) and both singletons (median 39 IQR 37.3–40 weeks of gestation, P = 0.2) and twins (median 36 IQR 34–37.2 weeks of gestation, P = 0.5). There were no statistically significant differences in the rates of GDM and IHCP between the study group and control groups.

Fig. 3B is a Kaplan-Meier curve comparing the cumulative incidence of placental-related adverse outcome between the late 2nd trimester selective termination group to that of the twins and singleton groups. The cumulative incidence of composite placental-related adverse outcome was earliest among twins and latest among singletons, with a statistically significant difference between these curves (P < 0.0001). The study group curve was located between that of twins and singletons, without a statistically significant difference between the study group's and both control groups' curves (P = 0.19 and P = 0.11).

4.5. Dichorionic late 2nd trimester selective termination

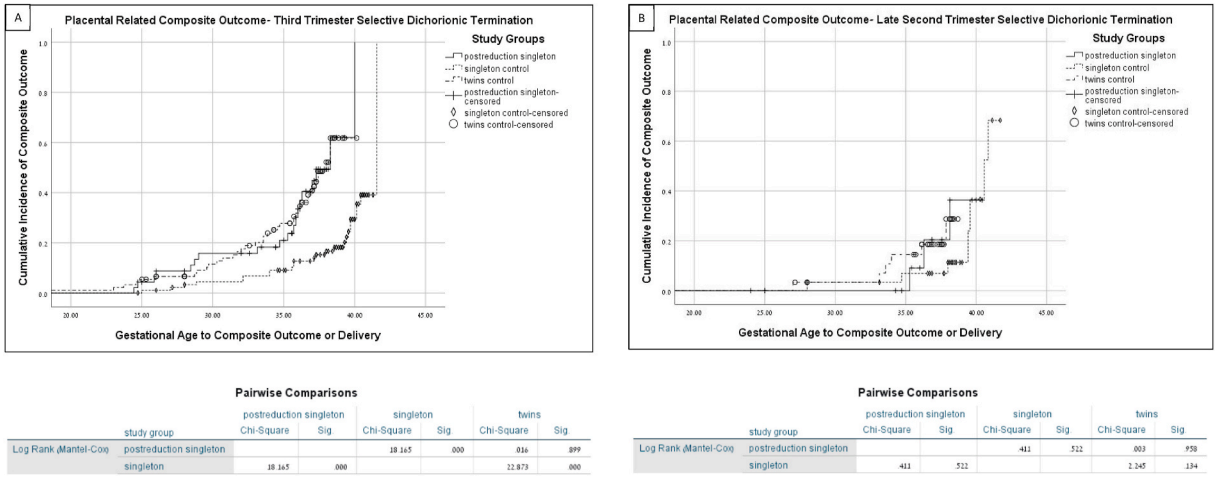
Table 4B and Fig. 4B exhibit the comparison of the rate, gestational

Table 4
Perinatal Outcome and Neonatal Adverse Outcome A. Third Trimester Termination Group (>28 weeks of gestation) B. Late 2nd Trimester Termination Group (20–27.6 weeks of gestation).

A	Third Trimester Selective Termination Group (N = 47)	Singleton Control Group (N = 94)	P value	Twin Control Group (N = 94)	P value[a]	P value[b]
Antenatal corticosteroids administration	85.1% (40/47)	5.6% (5/90)	**<0.0001**	18.7% (17/91)	**<0.0001**	**0.007**
Preterm Birth	61.7% (29/47)	17% (16/94)	**<0.0001**	45.7% (43/94)	0.07	**<0.0001**
Gestational age at Delivery (weeks)	36.4 (35.0–37.3)	39.1 (37.6–40.1)	**<0.0001**	37.0 (36.0–37.4)	0.7	**<0.0001**
Birth weight (grams)	2387 (2059–2809)	3025 (2740–3472)	**<0.0001**	2502 (2006–2806)	0.67	**<0.0001**
MOD NVD/VE	34% (16/47)	66% (62/94)	**<0.0001**	35.1% (33/94)	0.9	**<0.0001**
CS	66% (31/47)	34% (32/94)	**<0.0001**	64.9% (61/94)	0.9	**<0.0001**
RDS	6.4% (3/47)	1.1% (1/94)	0.1	6.4% (6/94)	1	0.12
Neonatal Composite Outcome	10.6% (5/47)	5.3% (5/94)	0.25	7.4% (7/94)	0.53	0.55

B	Late 2nd Trimester Selective Termination Group (N = 43)	Singleton Control Group (N = 86)	P value	Twin Control Group (N = 86)	P value[a]	P value[b]
Antenatal corticosteroids administration	37.2% (16/43)	5.8% (5/86)	**<0.0001**	14.3% (12/84)	**0.003**	**0.07**
Preterm Birth	41.9% (18/43)	14% (12/86)	**<0.0001**	43% (37/86)	0.9	**<0.0001**
Gestational age at Delivery (weeks)	37.1 (34.2–38.3)	38.6 (38.1–40.1)	**<0.0001**	37.2 (36.1–38.0)	0.2	**<0.0001**
Birth weight (grams)	2770 (2000–3220)	3153 (2807–3419)	**<0.0001**	2613 (2265–2940)	0.89	**<0.0001**
MOD NVD/VE	72.1% (31/43)	64% (55/86)	0.35	57% (49/86)	0.1	0.35
CS	27.9% (12/43)	36% (31/86)	0.35	43% (37/86)	0.1	0.35
RDS	11.6% (5/43)	3.5% (3/86)	0.07	2.3% (2/86)	**0.04**	1
Neonatal Composite Outcome	11.6% (5/43)	3.5% (3/86)	0.07	2.3% (2/86)	**0.04**	1

Data presented as Percentage (n/N) or Median (Interquartile Range).
Neonatal Composite Outcome include: Intraventricular Hemorrhage, Bronchopulmonary Dysplasia, Retinopathy of Prematurity, Necrotizing Enterocolitis, Respiratory Distress Syndrome, Neonatal Death.
GA, *Gestational Age*; MOD, *Mode of Delivery*; NVD, *Normal Vaginal Delivery*; VE, *Vacuum Extraction*; CS, *Cesarean Section*; RDS, *Respiratory Distress Syndrome*.
[a] Comparison between Selective Termination Study group and Twin Control group.
[b] Comparison between Singleton and Twin Control groups.



Pairwise Comparisons

		postreduction singleton		singleton		twins	
	study group	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	postreduction singleton			18.165	.000	.016	.899
	singleton	18.165	.000			22.873	.000

Pairwise Comparisons

		postreduction singleton		singleton		twins	
	study group	Chi-Square	Sig.	Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	postreduction singleton			.411	.522	.003	.958
	singleton	.411	.522			2.245	.134

Fig. 4. One Minus Survival Kaplan Meier curve comparing the cumulative incidence of placental related composite adverse outcome between A) post-3rd trimester selective dichorionic termination singletons and matched twins and singleton control groups B) post-late 2nd trimester selective dichorionic termination singletons and matched twins and singleton control groups.

age and cumulative incidence of composite placental-related adverse outcome of post-late 2nd trimester selective termination singletons originating from dichorionic pregnancies and their corresponding controls. The results were similar to late-second trimester selective termination comparison which included monochorionic originating pregnancies.

5. Perinatal and neonatal outcomes

5.1. Late selective termination (≥20 weeks)

Table S1 presents the comparison of perinatal and adverse neonatal outcomes between the whole study group and corresponding controls. Post-late selective termination pregnancies received significantly more steroids for fetal lung maturation than both the singleton (62.2% vs 5.7%, P < 0.0001) and twins groups (62.2% vs 16.6%, P < 0.0001). The remaining perinatal and neonatal outcomes showed statistically significant differences between the study and singleton groups and were all statistically similar between the study and twins groups. Post-late selective termination singletons had higher preterm birth rates (52.2% vs 15.6%, P < 0.0001), lower birthweights (2585 gr, IQR 2031–3065, vs. 3087 gr, IQR 2764–3427, P < 0.0001), higher cesarean delivery rates (47.8% vs 35%, P = 0.04), higher RDS rates (8.9% vs 2.2%, P = 0.01) and higher neonatal composite rates (11.1% vs 4.4%, P = 0.04), compared to singletons. Compared to twins, post-late selective termination singletons had higher rates of composite neonatal adverse outcome, at a borderline significance (11.1% vs 5%, P = 0.06).

5.2. Third trimester selective termination

Post-3rd trimester reduction singletons received significantly more steroids for fetal lung maturation than both the singletons (85.1% vs 5.6%, P < 0.0001) and twins (85.1% vs 18.7%, P < 0.0001) (Table S2A).

Compared to singletons, the 3rd trimester selective termination group, had a higher rate of prematurity (61.7% vs 17%, P < 0.0001), a lower birthweight (median 2387, IQR 2059–2809 gr vs median 3025, IQR 2740–3472 gr, P < 0.0001) and a higher rate of Cesarean delivery (66% vs 34%, P < 0.0001). There was no significant difference in the rate of composite neonatal adverse outcome or RDS, between the study and singleton groups.

Compared to the twins' group, there was a borderline significant trend of higher prematurity rate (61.7% vs 45.7%, P = 0.07). Otherwise, there were no statistically significant differences between the study and twins' group in terms of birthweight, mode of delivery and neonatal outcomes.

5.3. Late 2nd trimester selective termination

Post-late 2nd trimester reduction singletons received significantly more steroids for fetal lung maturation than both the singletons (37.2% vs 5.8%, P < 0.0001) and twins (37.2% vs 14.3%, P = 0.003) (Table S2B).

They had a higher rate of prematurity (41.9% vs 14%, P < 0.0001), lower gestational age at delivery (median 37.1, IQR 34.2–38.3 vs. median 38.6, IQR 38.1–40.1 weeks of gestation, P < 0.0001) and a lower birthweight (median 2770, IQR 2000–3220 gr vs median 3153, IQR 2807–3519 gr, P < 0.0001) compared to the singleton group. There were no statistically significant differences between the study group and the twins' group regarding these parameters. Despite a higher rate of steroid administration, neonates in the late 2nd trimester termination study group had a higher rate of composite neonatal adverse outcome compared to the twins' group (11.6% vs 2.3%, P = 0.04), and compared to singletons, at a borderline significance (11.6% vs 3.5%, P = 0.07). There was no statistically significant difference in the rate of Cesarean delivery among the study group and the singleton or twins' groups (27.9% vs 36%, P = 0.35, and 43%, P = 0.1, respectively).

6. Discussion

This retrospective case-control study of post-selective late termination (≥20 weeks of gestation) singletons highlights the effect of selective termination and its timing on the rate, gestational age and cumulative incidence of composite placental-related adverse outcome. Pregnant women who underwent a late selective termination, especially during the 3rd trimester had a cumulative incidence of composite placental-related adverse outcome similar to twins which presented significantly earlier and at a steeper incline compared to singletons. In contrast, pregnant women who underwent a late 2nd trimester selective termination had a cumulative incidence of composite placental-related adverse outcome which was comparable to singletons, resulting in a Kaplan Meier curve situated between the earlier rising twin curve and the later rising singleton curve. These observations suggest that performing a late selective termination, when indicated, from a twin to a singleton pregnancy during the second trimester might offer an advantage of a delayed occurrence of placental-related adverse outcomes, contrary to a 3rd trimester selective termination. This appears to be applicable for selective termination, regardless of original chorionicity. This unique model of twin pregnancy reduced to a singleton pregnancy, at different trimesters, provides an opportunity to explore the temporal relationship between the timing of the procedure and its effect on the occurrence of placental related adverse outcome, revealing novel insights.

6.1. Interpretation of data

To the best of our knowledge this study is the first to address the association between the gestational age at time of selective termination and the presentation of placental-related adverse outcomes. Previous studies on fetal reduction and selective fetal termination have focused on its effect on the length of pregnancy, complications of prematurity and procedure related complications [28–37].

The findings of the present study further support the observation that multiple pregnancies are more prone to placental-related adverse outcomes and at an earlier stage in pregnancy, than singleton gestation [6–9] and suggest a possible advantage for an earlier selective fetal termination. These findings enhance our knowledge on the relationship between plurality and placental-related complications.

6.2. Clinical implications

In addition to the delayed increase in the cumulative incidence of placental-related adverse outcome, there are a few more advantages to selectively terminating during the late 2nd trimester than in the third trimester. While selective termination during the 3rd trimester was associated with a significantly higher rate of Cesarean delivery compared to matched singletons, and comparable to that of twins, post-late 2nd trimester selective termination singletons had a significantly lower rate of the Cesarean delivery, which was comparable to singletons. The implicit promise of this decline in the rate of Cesarean delivery is a reduction in maternal morbidity and mortality in the index pregnancy [38,39] as well as in subsequent pregnancies [40–43]. An additional advantage to selectively terminating in the late 2nd trimester, compared to the 3rd trimester is an improved perinatal outcome. In both subgroup comparisons, there was a higher rate of preterm delivery, earlier gestational age at delivery and lower birthweight in the study group compared to singletons. However, these differences were more profound in the 3rd trimester selective termination subgroup.

The most significant disadvantage of selectively terminating in the late 2nd trimester, as demonstrated in the present study, was the rate of pregnancy loss which was 6.5% (3/46), compared to none in the 3rd trimester. Of note, pregnancy loss occurred only in monochorionic pregnancies requiring a more invasive method of selective termination, such as radiofrequency ablation or bipolar ligation, compared to

potassium chloride injection in dichorionic twins [44].

6.3. Strengths and limitations

The strengths and limitations of the study should also be discussed. To the best of our knowledge, this is the first study to address the association of late selective termination from twins to singletons and the prevalence of placental-related adverse outcomes and other perinatal parameters. As this is a single center study, there was a standardization of the management and we were able to thoroughly examine all medical charts and exclude cases that did not meet inclusion criteria. Moreover, the meticulous matching for other known placental related adverse outcome risk factors, as well as the inclusion of two control groups, enabled an isolated and comprehensive comparison of the presentation of placental insufficiency between late selective termination singleton pregnancies and matched singletons and twins. The limitations of the study should also be acknowledged. The case control study design precludes comment on causality. In addition, the study groups included both types of twin chorionicities. This might have added bias rooted in differences in complication profiles, pregnancy management and method of selective termination. However, since monochorionic and dichorionic twins did not differ significantly in the rate and timing of placental-related adverse outcome or in the latency period between selective termination and delivery (Table S3), the inclusion of monochorionic twins was reasonable and provided a larger cohort, increasing the study's power and enabling stratification to trimester at time of procedure. A sub-analysis of selective dichorionic termination and controls showed similar results to that of the combined chorionicity study group, supporting this strategy (Table and Fig. 4). Finally, due to the rarity of stillbirth, the study was not powered to assess the association, if such exists, of late selective termination singletons and stillbirth.

7. Conclusion

To conclude, the cumulative incidence of placental-related adverse outcome among third trimester selective termination singletons is similar to that of twins, characterized by a statistically significant earlier and steeper rise in the occurrence of placental related complications compared to singletons. An earlier selective termination performed in the late 2nd trimester is associated with a delayed rise in the cumulative incidence of placental-related complications and a decreased rate of cesarean delivery, comparable to singletons.

The findings of the present study further support existing evidence of an association between multiple pregnancy and placental-related adverse outcome and enhance our knowledge by demonstrating the beneficial effect of an earlier selective termination on the manifestation of placental related complications. These findings may be of clinical importance when determining the optimal gestational age to perform a late selective termination.

We declare to have fulfilled the following roles in the conduct of the study and composing of the manuscript and to have seen and approved the final version

Tal Weissbach: Project administration, Writing - Original Draft, Investigation, Formal analysis.

Inbal Tal: Writing - Review & Editing, Investigation, Visualization.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2022.02.011.

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