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### Challenges in spontaneous preterm birth

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# 2



## Trends in preterm birth in singleton and multiple gestations in the Netherlands 2008-2015: a population-based study

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## **ABSTRACT**

### **Objective**

Preterm birth is the most important cause of perinatal morbidity and mortality. Over the past years several preventive measures have been studied and implemented. Preterm birth percentage in 2015 in the Netherlands was 6.9%, according to data from the European Peristat project, reporting on perinatal health in Europe. Various preventive measures might have influenced the incidence and outcome of preterm birth. Our aim was to give an overview of the trends in preterm births for both singleton and multiple gestations in the Netherlands in order to guide future research.

### **Study design**

We studied a nationwide cohort including both singleton and multiple gestations without congenital anomalies between 2008 and 2015. Outcomes were total preterm birth (defined as birth before 37 weeks of gestation), spontaneous and iatrogenic preterm birth < 37 weeks, spontaneous and iatrogenic preterm birth percentages between 34-36 weeks, 32-34 weeks, 28-31 weeks and  $\leq 27$  weeks using a moving average technique. Trend analysis was performed using the Cochran Armitage test. Singleton and multiple gestations were analyzed separately.

### **Results**

Our final study population comprised 1,303,786 women with a singleton and 44,951 women with a multiple pregnancy. Preterm birth < 37 weeks in singletons decreased from 5.6% in 2008 to 5.3% in 2015 ( $P < 0.0001$ ), in both spontaneous and iatrogenic preterm birth. Preterm birth  $\leq 27$  weeks increased from 0.40% to 0.45% ( $P$  for trend  $< 0.0001$ ).

The number of multiple gestations decreased over the years, as well as the percentage of multiples conceived through IVF/ICSI. There was an increase in total and iatrogenic preterm birth < 37 weeks from 36.7 - 38.2% ( $P < 0.0001$ ) in multiples. The number of multiples < 32 weeks decreased, in both the spontaneous and iatrogenic group.

### **Conclusion**

In the Netherlands preterm birth risk in singletons decreased between 2008 and 2015 but an increase was noted in preterm birth  $\leq 27$  weeks. In multiples the total preterm birth risk increased, due to an increase in indicated preterm birth.

## INTRODUCTION

Preterm birth, defined as delivery before 37 completed weeks of gestation, is a major cause of both perinatal mortality and morbidity<sup>1</sup>. Children born after an indicated or spontaneous preterm birth suffer more often from both psychological and developmental disabilities as compared to children born at term.

Spontaneous preterm birth (PTB) is a complex syndrome with multiple etiologies. Even though this has been recognized for several years now, we have failed to clearly define subgroups and take this knowledge into account in performing research and trials. Trend analysis can help notice certain patterns in preterm birth which can help in defining subgroups in preterm birth that needs more attention in future research. Previous research not always adequately separates trends in multiple and singletons making the results more difficult to interpret, only reports on singletons, or did not use recent data.<sup>2-5</sup>

In 2011 a study using data from the Dutch Perinatal registry between 2000-2007 reported a decline in preterm birth risk in singletons from 6.4% in 2000 towards 6.0% in 2007 ( $P < 0.0001$ ). In multiple pregnancies a small increase in preterm birth was present (47.3% vs. 47.7%,  $p = 0.047$ ) in the same period, mainly due to increased number of indicated birth in this group (15.0% in 2000 up to 17.9% in 2007,  $p < 0.0001$ ).<sup>6</sup> No new data have been published since this last report in 2011 on PTB trends in the Netherlands. A European study on PTB trends dates from 2013.<sup>7</sup>

It has been hypothesized that implementation of various preventive measures over the past years might have influenced the incidence and outcome of PTB within the Netherlands. Our aim was to describe trends in PTB in the Netherlands between 2008 and 2015, separate for singletons and multiple pregnancies.

In addition, we assessed the total number of multiple pregnancies, since the total burden of preterm birth in multiple pregnancies not only depends on the prevalence of preterm birth but also on the total number of multiples born per year.

## MATERIAL AND METHODS

This study was a population-based cohort study using data from the Dutch Perinatal registry (PERINED) from 2008 to 2015. The PERINED registry collects data on all births (live births and stillbirths) above 22 weeks of gestation and a birthweight above 500 g. It contains information on pregnancy complications, deliveries and hospital (re)admissions until 28 days after birth. Anonymous data

regarding pregnancies and birth outcomes is obtained by a validated linkage of three registries. These are the midwifery registry, the obstetric registry and neonatal registry (LVR-1, LVR-2 and LNR respectively). PERINED authorized the usage of records and analysis of the obtained data for the purpose of this study, (approval no. 15.44). Caregivers enter the data in this national registry during prenatal care, delivery and neonatal period. Annually these data are sent to the office of PERINED and checked for among others; ranges and consistency. The registry covers over 96-98% of all births in the Netherlands<sup>8</sup>. The PERINED registry is used primarily for an annual assessment of the quality indicators of obstetric care. In addition, data from this national database has been used extensively in other peer-reviewed research. No institutional review board approval or informed consent was obtained for this study since the use of this data was within boundaries set by Dutch law on the use of registry data.

Since 2010 gestational age was based on Crown Rump Length (CRL) measured during first-trimester ultrasound. From 2008, CRL was already commonly used throughout the country. If no first trimester scan was performed between 2008 and 2010, gestational age was based on date of the last menstrual cycle or second trimester scan. This was in concordance with the national guideline<sup>9</sup>.

In pregnancies established by artificial reproductive techniques (ART), dates of intra-uterine insemination or oocyte pickup were used for dating.

### **Inclusion and exclusion criteria**

All births registered in PERINED between Jan. 1, 2008 until Dec. 31, 2015 were selected for this study. Pregnancies complicated by congenital abnormalities or with an unknown gestational age at delivery were excluded from the analysis. For the analysis on trends of preterm birth we additionally excluded pregnancies with an intrauterine fetal death.

### **Outcome Measures**

The primary outcome was PTB before 37 weeks of gestation. Secondary outcomes were spontaneous and iatrogenic PTB risk < 37 weeks and PTB percentages between 34-36 weeks, 32-33 weeks, 28-31 weeks and  $\leq$  27 weeks of gestation stratified for spontaneous and indicated start of labor. In multiples, additionally the mode of conception was assessed.

### **Statistical analysis**

Singleton and multiple gestations were reported separately, because of their known differences in gestational age at birth and risk for PTB. For baseline characteristics, we divided the cohorts into two time periods (2008-2011 and 2012-2015). We compared baseline characteristics using univariate analyses

with the Student *t*-test for the continuous variables and the Chi-square test for the categorical variables. We used a moving average technique covering three gestational weeks per measurement to correct for possible fluctuations due to the small number of events. To investigate whether there was a trend in PTB risk over time, we performed a Cochran-Armitage trend test, with the year as the independent variable and preterm birth risk as the dependent variable. In singletons this was performed for PTB < 37 weeks and for the subgroups of PTB 34-36 weeks, 32-33 weeks, 28-31 weeks and  $\leq 27$  weeks of gestation.

In multiple pregnancies this test was performed to test for a trend in the total number of multiples and for the percentage of multiples conceived through ART (in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)). In addition we tested the trend for PTB < 37 and < 32 weeks in the total group and separate for spontaneous and indicated PTBs.

Data were analyzed using SAS software (SAS Institute Inc., Cary, NC, USA version 9.4). Statistical significance was set at a threshold of 0.05.

Permission was given by PERINED, the Dutch perinatal registry, to use records and analyze data for the purpose of this study (approval no 15.44)

## RESULTS

### Study population

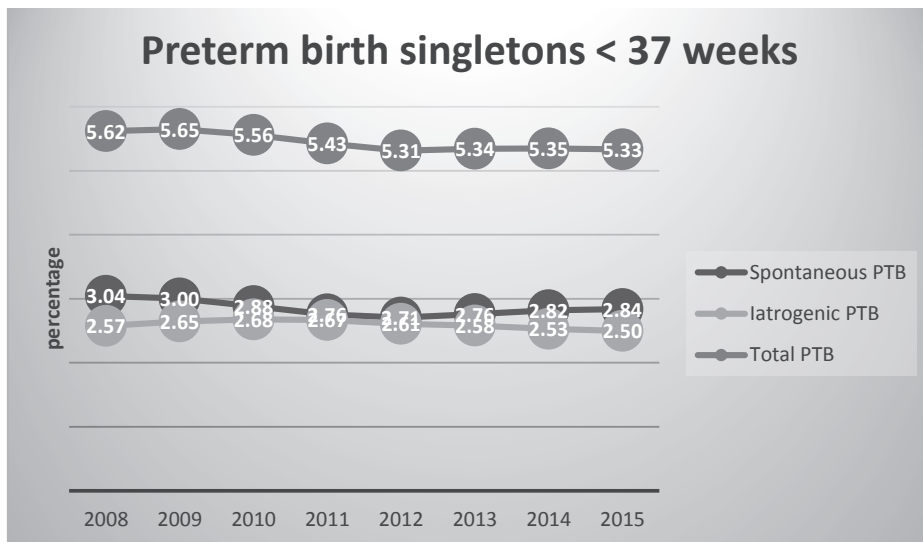
Our final study population comprised of 1,348,737 births of which 1303,786 women with a singleton pregnancy and 44,951 women with a multiple pregnancy.

### Singleton pregnancies

Our findings of the singleton population are presented in Table 1.

The total PTB percentage < 37 weeks in singleton pregnancies dropped from 5.6% in 2008 to 5.3% in 2015,  $p < 0.001$ , a trend that was seen in both spontaneous (3.0% - 2.8%,  $p < 0.001$ ) as iatrogenic preterm birth (2.6% - 2.5%,  $p < 0.001$ ) (Figure 1).

Figure 2 shows the preterm birth trends for PTB  $\leq 27$  weeks of gestation, 28-31 weeks, 32-33 weeks and 34-36 weeks. The percentage of very early PTB  $\leq 27$  weeks increased from 0.40% in 2008 to 0.45% in 2015 ( $P$  for trend  $< 0.0001$ ), due to an increase in both very early spontaneous as iatrogenic PTB. From 32 weeks onwards, the percentage of PTB decreased over the years, mainly in the weeks 34-36 from 6.5% to 6.0% ( $P$  for trend  $< 0.0001$ ). This trend is present in both iatrogenic as in spontaneous late PTB.



**Figure 1:** Preterm birth risk in singletons < 37 weeks

**Table 1:** Baseline characteristics of singleton pregnancies in the years 2008-2011 and 2012-2015

	2008-2011 (N=664,964)		2012-2015 (N=638,822)	
		% *		% *
<b>Maternal characteristics</b>				
Maternal age (mean, SD)	30.7	5.0	30.9	5.0
Primiparous	306,093	46	286,885	45
IVF/ICSI §	6,329	0.95	7,157	1.1
Hypertensive disorders #	61,270	9.2	71,314	11
<b>Outcomes</b>				
Intra-uterine fetal death	2,801	0.42	2,206	0.35
Start of delivery				
Spontaneous	365,608	55	325,541	51
Induction	255,900	39	266,055	42
Elective caesarean	43,456	6.5	47,226	7.4
Birthweight (mean, SD)	3,454	580	3,431	564

\*Variables are noted as N and% unless described otherwise

§ In vitro fertilization / Intracytoplasmic sperm injection

#Pre-gestational hypertension, pregnancy induced hypertension and pre-eclampsia

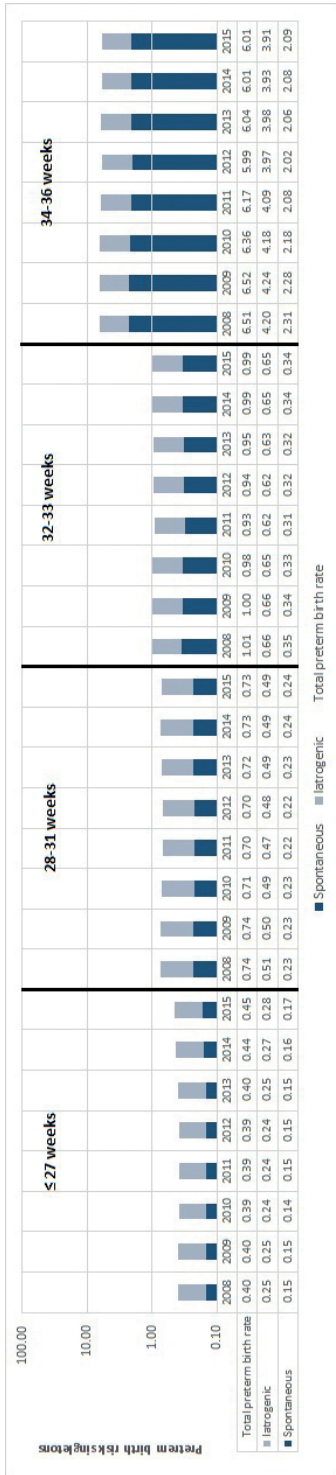


Figure 2: Trend in total, spontaneous an iatrogenic preterm birth for four gestational age subcategories among singletons



Furthermore, there is a notable increase in pregnancies conceived through IVF or ICSI from 0.95% in the years 2008-2011 to 1.1% in the years 2012-2015. Also, the number of hypertensive disorders increased from 9% to 11% (Table 1).

### Multiple pregnancies

The results of the multiple gestations are shown in Table 2.

The total percentage of PTB in multiples < 37 weeks increased from 50.9 - 52.5% (p for trend <0.0001). This was due to an increase in iatrogenic PTB from 36.7 - 38.2% (P < 0.0001) since the risk of spontaneous PTB < 37 in multiples remained stable over the 8-year study period from 14.2 - 14.3% ( Figure 3).

In addition, the risk of PTB in multiples < 32 weeks decreased from 9.3 - 8.6% (P < 0.0001). This decreasing trend was present in both spontaneous as iatrogenic PTB in multiples <32 weeks (Figure 3).

The percentage of multiple gestations significantly decreased (P < 0.001) in the period 2008-2015 (3.6% to 3.2%) (Supplemental Figure 1). In 2008 6,251 multiples were registered, compared to 5,132 multiple gestations in 2015. The contribution of ART such as IVF and ICSI to the number of multiple gestations also declined, p for trend < 0.001 (Supplemental Figure 1).

Furthermore, in concordance with the singleton population an increase in hypertensive disorders is present from 17% in 2008-2011 to 21% in 2012-2015.

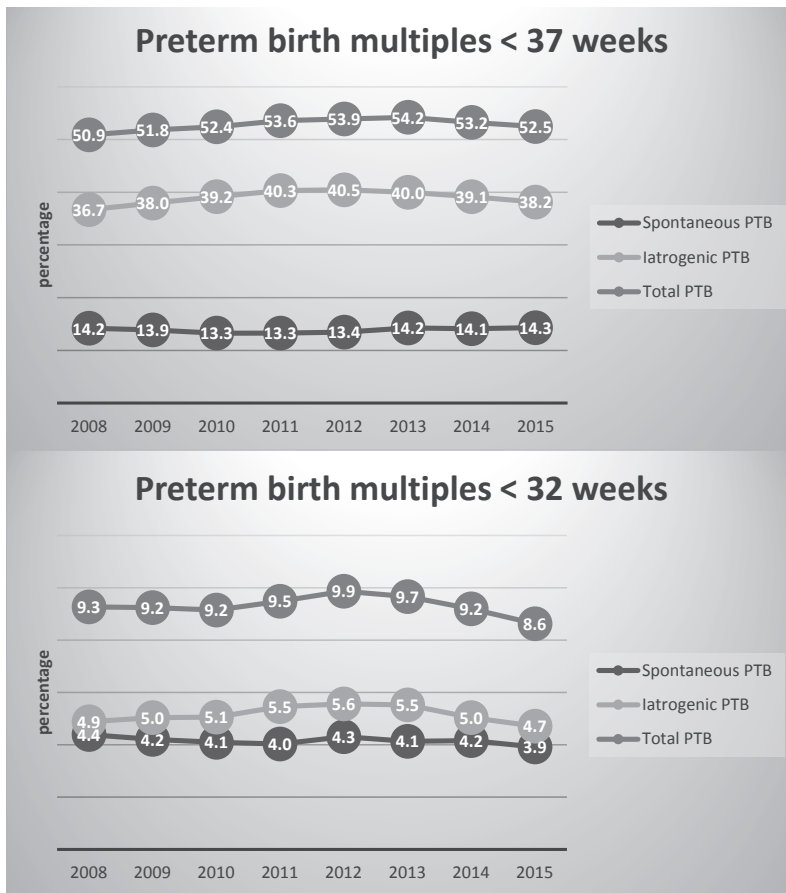
**Table 2:** Baseline characteristics of multiple pregnancies in the years 2008-2011 and 2012-2015

	2008-2011		2012-2015	
	(N=23,640 neonates)	% *	(N=21,311 neonates)	% *
<b>Maternal characteristics</b>				
Maternal age (mean, SD)	31,9	4,8	31,9	5,0
Primiparous	11197	47	9932	47
ART §	2233	9,5	1407	6,6
Hypertensive disorders#	4048	17	4567	21
<b>Outcomes</b>				
Intra-uterine fetal death	323	1,4	272	1,3
Start of delivery				
Spontaneous	4236	18	3871	18
Induction	13746	58	11871	56
Elective caesarean	5658	24	5569	26
Birthweight (mean, SD)	2410	632	2388	628

\* Variables are noted as N and % unless described otherwise

§ In vitro fertilization / Intracytoplasmic sperm injection

# Pre-gestational hypertension, pregnancy induced hypertension and pre-eclampsia



**Figure 3:** Preterm birth risk in multiples < 37 weeks and < 32 weeks

**COMMENT**

**Principal findings**

Our study showed a significant decrease in the total PTB risk in singletons < 37 weeks in the period 2008-2015. Subdivided by gestational age, this total decrease was due to a decrease in the number of PTBs between 32 and 37 weeks. In contrast, a subtle increase in very early PTB ≤ 27 weeks was noted. Even though this increase did not lead to an increase in the total number of PTB in singletons, this increase is important since it highlights a group with the most serious consequences for neonatal outcome, and subsequently requires more attention.

For multiples the total number of PTB < 37 weeks significantly increased, however the number spontaneous PTB < 32 weeks and iatrogenic PTB < 32 weeks decreased significantly. We found a decrease in the total percentage and number of multiples and a decrease in the number of multiples conceived through IVF/ICSI.

### **Relationship to other studies**

Our study is a sequel to the study by Schaaf et. al. <sup>6</sup> that also used the PERINED database and included 1,451,246 pregnancies in the previous time period (2000-2007). Schaaf and colleagues reported a decreasing trend in PTB percentages in singletons as opposed to studies from the United States and Scotland.<sup>10,11</sup> Our study shows a persistent decrease in both iatrogenic and spontaneous preterm birth in singletons from 32 weeks onwards. Our results are in concordance with a recent report from Gyamfi-Bannerman et. al <sup>5</sup> where trends in both spontaneous and iatrogenic PTB in singletons over the period 2005-2010 were described. Schaaf et. al <sup>6</sup> noticed an increase in the number of iatrogenic preterm births in multiples. In our cohort this trend is continued.

No other study addressed recent preterm birth trends among multiple gestations.

In both singleton and multiple pregnancies we noticed a rise in women with hypertensive disorders over the years. This trend was also observed in other populations. <sup>12,13</sup>

### **Strengths and limitations**

Our study has both strong and weak points. A strength of our study is that we used data from a large well-maintained database that covers over 96-98% of all births in the Netherlands. Therefore we are able provide a reliable overview of PTB risk within the Netherlands. The large sample size makes it possible to report on singleton and multiple gestations separately and to specify spontaneous and iatrogenic start of labor.

A limitation of the study is the fact that a dating protocol for the determination of the gestational age was officially introduced nationwide in 2010. <sup>9</sup> However also in the previous years the vast majority of women received a first trimester ultrasound for confirmation of the estimated due date. Therefore we feel confident that the possible confounding of erroneous dating is limited. In addition, the majority of our data in this study are on pregnancies beyond 2010.

### **Clinical implications**

Our study showed a decrease in spontaneous PTB in both singletons and multiples between 2008 and 2015. Women who had prior preterm birth are offered 17-OH progesterone as part of the national protocol 'Prevention of

recurrent spontaneous preterm birth.<sup>14</sup> Our results might be influenced by the introduction of this national protocol in 2007. Furthermore, screening for short cervix in this high-risk population and ultrasound-indicated cerclages have been implemented nationwide. A similar trend analysis in a longitudinal linked database including the years before and after 2007 would be interesting to evaluate this implementation. In addition, several other randomized controlled trials on preterm birth were conducted in the Netherlands in the included time period<sup>15-17</sup>. What the individual effect of these studies was on the reduction of PTB cannot be deduced from this study but can be researched in the future. Previous research indicates that the effect of these interventions on a population level might be rather limited since the complex underlying etiology of PTB is still unresolved<sup>18</sup>.

Our data show a subtle increase in the number of preterm birth  $\leq 27$  weeks in singletons. Implementation of previous preventive strategies might have shifted the gestational age at birth with a few days/weeks. This might result in a decrease in immature deliveries. Moreover since 2006 neonates from 25 weeks onwards get active support after delivery and since 2010 this has shifted to 24 weeks gestational age. This might reflect in the decrease of intra-uterine death in singletons (0.42 vs. 0.35,  $P < 0.0001$ ) (Table 1)) and an increase in early preterm births ( $\leq 27$  weeks).

### **Research implications**

In singletons, the total PTB percentage  $\leq 27$  weeks increased, as a result of an increase in both iatrogenic as well as spontaneous preterm birth. It is known that PTB is not one disease but rather a syndrome that can have different etiologies such as infection, cervical disease, vascular disease and more. Perhaps the interventions and studies performed in this time period are only able to target some of these etiologies and not all. It could be hypothesized that we are at the moment less capable of influencing very early preterm birth. We think further research is warranted in order to gain more insight in the different etiologies of PTB and their contribution to preterm birth at different gestational age categories. In addition, future meta-analysis on interventions should try to find out if the intervention works for all preterm birth etiologies or just for one. For instance, perhaps pessary is effective mainly in women with an incompetent cervix whereas progesterone promotes myometrial quiescence and thereby reduces the risk of preterm birth.

We observed a decline in the overall number of multiple gestations as well as a strong decrease in the number of multiples conceived through IVF/ICSI, possible due to the introduction of a single-embryo-transfer (SET) policy in IVF/ICSI procedures. This might be beneficial in the prevention of PTBs since a multiple gestation is a strong risk factor for preterm birth. Guidelines for the management

of monochorionic twins have changed over the past years, since 2011 it has been suggested to induce labor between 36-37 weeks as opposed to 37 weeks in the previous time period <sup>19</sup>. The trend of higher numbers of iatrogenic PTB in multiples asks for further research on the necessity of iatrogenic preterm delivery.

## **CONCLUSION**

In the Netherlands there is a decreasing trend in PTB < 37 weeks in singletons in both spontaneous and iatrogenic births. An increase in early preterm birth  $\leq$  27 weeks in singletons was noted in both the iatrogenic and spontaneous group. There is an increase in total PTB in multiples, mainly as a result of increased iatrogenic PTB.

Further research should focus on the better understanding of the underlying mechanism of spontaneous PTB and the possible differences in effectiveness of interventions on these underlying mechanisms. In addition, future research should focus on the necessity for late iatrogenic preterm birth in multiples.

## **ACKNOWLEDGEMENTS**

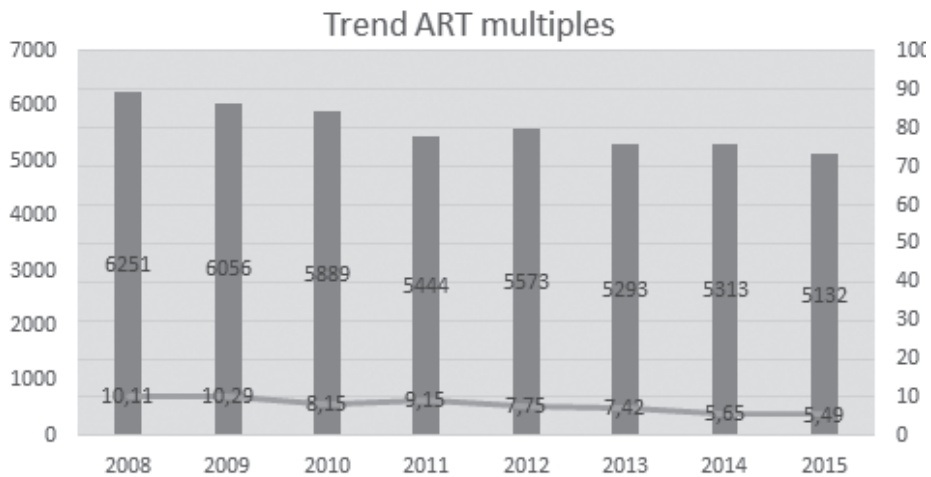
We would like to thank all Dutch midwives, obstetricians, neonatologists and other perinatal healthcare providers for the registration of perinatal information and the Foundation of The Netherlands Perinatal Registry (<https://www.perined.nl>) for permission to use the registry data.

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## Chapter 2

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**Supplemental Figure 1:** Number of multiple pregnancies and percentage conceived through ART