# Pregnancies in Women Aged 45 Years and Older – a 10-Year Retrospective Analysis in Berlin

# Schwangerschaften bei Frauen im Alter von 45 Jahren und älter – eine retrospektive Analyse über einen Zeitraum von 10 Jahren in Berlin

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## ABSTRACT

**Introduction** Improved fertility treatment options and a change in the socio-cultural concept of family planning, especially in industrialized regions, has led to an increasing number of births by women of advanced maternal age, which is associated with a higher rate of complications. The aim of this study was to analyze pregnancy outcomes in women aged ≥ 45 years in an inner-city German hospital and to compare these results to those of a younger cohort.

**Materials and Methods** Over a 10-year period from January 2004 to May 2015, the pregnancy outcomes of all 186 women aged ≥ 45 years who delivered in our hospital were compared in a 1 : 1 ratio to those of a cohort of 29-year old women.

**Results** The rates of assisted reproduction (34 vs. 3 %), multiple pregnancies (16 vs. 5 %) and cesarean section (59 vs. 29 %) were significantly increased in the study group. There was an increased risk of preterm delivery (28 vs. 11 %), preeclampsia, gestational diabetes and premature rupture of membranes in the advanced maternal age group.

**Conclusion** Advanced maternal age leads to higher rates of fetal and maternal complications. These findings should be taken into account when planning assisted reproduction and obstetrical care in women with advanced maternal age.

## ZUSAMMENFASSUNG

**Einleitung** Die Verbesserungen bei der Auswahl an Fruchtbarkeitsbehandlungen und der soziokulturelle Wandel in der Familienplanung hat, besonders in den industrialisierten Ländern, zu einer zunehmenden Anzahl an Geburten bei Frauen im fortgeschrittenen Alter geführt, was mit einer höheren Komplikationsrate verbunden ist. Ziel dieser Studie war es, den Schwangerschaftsverlauf bei Frauen im Alter von ≥ 45 Jahren zu analysieren, die in einem innerstädtischen deutschen Krankenhaus entbunden hatten, und die Ergebnisse mit denen einer jüngeren Frauenkohorte zu vergleichen.

**Material und Methoden** Die Schwangerschaftsverläufe aller 186 Frauen im Alter von ≥ 45 Jahren, die in unserer Klinik in einem Zeitraum von 10 Jahren zwischen Januar 2004 und Mai 2015 entbunden hatten, wurden in einer 1 : 1-Ratio mit denen einer Kohorte von 29-jährigen Frauen verglichen.

**Ergebnisse** Die Raten für künstliche Befruchtung (34 vs. 3 %), Mehrlingsschwangerschaften (16 vs. 5 %) und Sectio caesarea (59 vs. 29 %) waren signifikant höher in der Gruppe der Spätgebärenden. In der Studiengruppe war das Risiko für Frühgeburten (28 vs. 11 %), Präeklampsie, Gestationsdiabetes und vorzeitigen Blasensprung ebenfalls erhöht.

**Schlussfolgerung** Ein höheres mütterliches Alter bei der Schwangerschaft ist mit höheren Komplikationsraten für Mutter und Kind verbunden. Diesem Ergebnis sollte bei der Planung assistierter Reproduktion sowie bei der geburtshilflichen Planung für Mütter im fortgeschrittenen Alter Rechnung getragen werden.

## Introduction

Over the last five decades, the mean maternal age at birth in Germany has increased steadily from an average age of 27.5 years in 1960 to 30 years in 2014 [1]. The birth-rate of women aged ≥ 40 years has also increased slightly, with 35 559 births in 2014 compared to 34 923, 34 641 and 34 203 in the years 2011 to 2013, respectively [2].

This mirrors the dramatically increasing worldwide rate of women of advanced maternal age giving birth over the last dec-

ades [3]. In 1991, 19/1000 pregnancies were in the age group 40–44 years. This rate had increased to 61/1000 births in 2013.

With the introduction of assisted reproduction technologies, women have the possibility of postponing family planning. Especially in industrialized nations, women and couples can decide and have decided to postpone marriage and family planning, mostly for career reasons. The prolonged system of education, career priorities, and the fact that contraception is common and easily available have contributed to this recent shift.

In the USA the rate of primigravidae aged 35–39 has steadily increased since the 1970s. The rate for women aged 40–44 remained steady in the 1970s and began to increase significantly later on in the 1980s and has more than doubled from 1990 to 2012 [4]. In Germany, the mean age for women undergoing IVF (in-vitro fertilization) increased from 31 years in 1997 to 35 years in 2014; the mean partners' age has likewise increased, from 35 to 38 years [5].

It is well documented that maternal and fetal complications occur more frequently with advanced maternal age [6]. Furthermore, maternal co-morbidities such as hypertension or diabetes are also more common due to the age-dependent onset of these diseases. Studies show that mothers aged 35 years or older at the time of giving birth had a 30% higher risk of preterm birth, particularly in low- and middle-income countries [7, 8]. Moreover, cesarean section rates for pregnancies in this age group are higher, as are the prevalence of gestational diabetes, hypertension, decreased fetal birth weight, preterm delivery and stillbirths [9–11]. Pawde et al. showed that adverse outcomes such as preeclampsia and placental abruption occurred significantly more often in women with advanced maternal age of ≥ 35 years and that the rate of assisted conception was significantly higher [12]. The majority of studies looked at patients aged > 35 years, with a few focusing on women over the age of 40. There is, however, a paucity of studies on pregnancies in the very advanced maternal age group of ≥ 45 years, which is why we decided to focus on this subgroup. Schoen et al. reviewed 16 studies on maternal and perinatal risks for women over 44 years of age in industrialized nations. They concluded that pregnancy-induced hypertension and gestational diabetes were more likely to occur in older gravidae. The cesarean rate was higher (RR = 4.1), and perinatal mortality was also higher (RR = 2.4) in the investigated cohort [13].

The aim of this study was to analyze maternal and fetal outcomes of pregnancies in women aged ≥ 45 years and compare them to those of a low-risk group in terms of maternal age, in an inner-city Berlin hospital.

# Materials and Methods

## Study group

We retrospectively analyzed all (n = 186) women aged 45 years and older who gave birth at the Charité University Hospital Berlin, Campus Mitte and Campus Virchow Klinikum, between January 2004 and May 2015. The subjects were identified electronically in our birth records system.

## Control group

Patients who met the criteria for the control group and had given birth in the same time period as the study group were randomly selected from the hospital computer system database. This was done to allow an equal statistical comparison of the study group with the control group (1 : 1 ratio).

Data was collected from patient files and the hospital-validated electronic databases (ViewPoint Perinatal Information System and SAP).

## Outcome parameters

Outcomes to be analyzed included the occurrence of maternal or fetal complications such as preeclampsia (PE, defined as new onset of elevated blood pressure > 140/90 mmHg and proteinuria ≥ 0.3 g in a 24-hour urine collection), intrauterine growth restriction (IUGR, defined as a pathological fetal growth restriction below the 10th percentile), gestational diabetes (GDM, defined as glucose intolerance with onset during pregnancy), preterm rupture of membranes, chorioamnionitis, cervical shortening, preterm placental abruption, placenta previa, velamentous cord insertion, adherent placenta, and number of multiple pregnancies, mode of delivery, blood loss, birth weight, and duration of pregnancy.

## Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (IBM SPSS Statistics Version 22, IBM Corporation, USA). Descriptive analyses were done for continuous and categorical variables. Means ± standard deviation are given for continuous variables; frequencies (%) are given for categorical variables. Test selection was based on the evaluation of the variables for normal distribution. Continuous variables were then compared using the two-tailed Student's t-test. Categorical variables were compared using the $\chi^2$-test or Fisher's exact test, as appropriate. P-values for all variables were two-sided and statistical significance was set at $p \leq 0.05$.

# Results

In the period from January 2004 to May 2015 a total of 53 546 women gave birth at the Charité University Hospital Berlin. Of these, 1237 women were in the age group ≤ 18 years (2.3%), 23 195 in the age group 19–29 years (43.3%), 26 137 in the age group 30–39 years (48.8%) and 2791 were 40 to 44 years old (5.2%). 186 patients were aged ≥ 45 years at the time of giving birth (0.34%). In 2004 only 4 women aged ≥ 45 years gave birth compared to 18 women in 2014. In the years 2004–2009 an average of 12 women aged ≥ 45 gave birth at our clinic; in the years 2010–2015 this number increased to an average of 19 women per year.

## Study group

The ages of the n = 186 analyzed subjects varied from 45 to 65 years, although the majority of subjects (46%) were 45 years old, and 23% were 46 years old. Gravidity ranged from 1 to 16 with a mean of 4.2 ± 2.6. Parity ranged from 0 to 13 with a mean

▶ **Table 1** Patient characteristics and co-morbidities for the study and control groups.

| | Study group (n = 186) | Control group (n = 186) | |
|---|---|---|---|
| Maternal age (years, range) | 46.56 ± 2.66 (45–65) | 29 | **p < 0.001** |
| Gravidity (range) | 4.2 ± 2.6 (1–16) | 2.3 ± 1.5 (1–8) | **p < 0.001** |
| Parity (range) | 2.8 ± 2.1 (0–13) | 1.8 ± 1.1 (0–7) | **p < 0.001** |
| Co-morbidities | | | |
| ▪ Hypertension | 13 | 0 | **p < 0.001** |
| ▪ Enucleation of uterine fibroids | 10 | 0 | **p < 0.001** |
| ▪ Depression | 2 | 1 | p = 1.000 |
| ▪ Breast cancer | 2 | 0 | p = 0.498 |
| ▪ HIV | 2 | 0 | p = 0.498 |
| ▪ Hepatitis B | 4 | 1 | p = 0.371 |
| ▪ Epilepsy | 2 | 1 | p = 1.000 |
| ▪ Cervical conization | 4 | 3 | p = 1.000 |
| ▪ Cardiac arrhythmias | 3 | 3 | p = 1.000 |
| Cesarean section in a previous pregnancy | 33 (18%) | 20 (11%) | p = 0.074 |

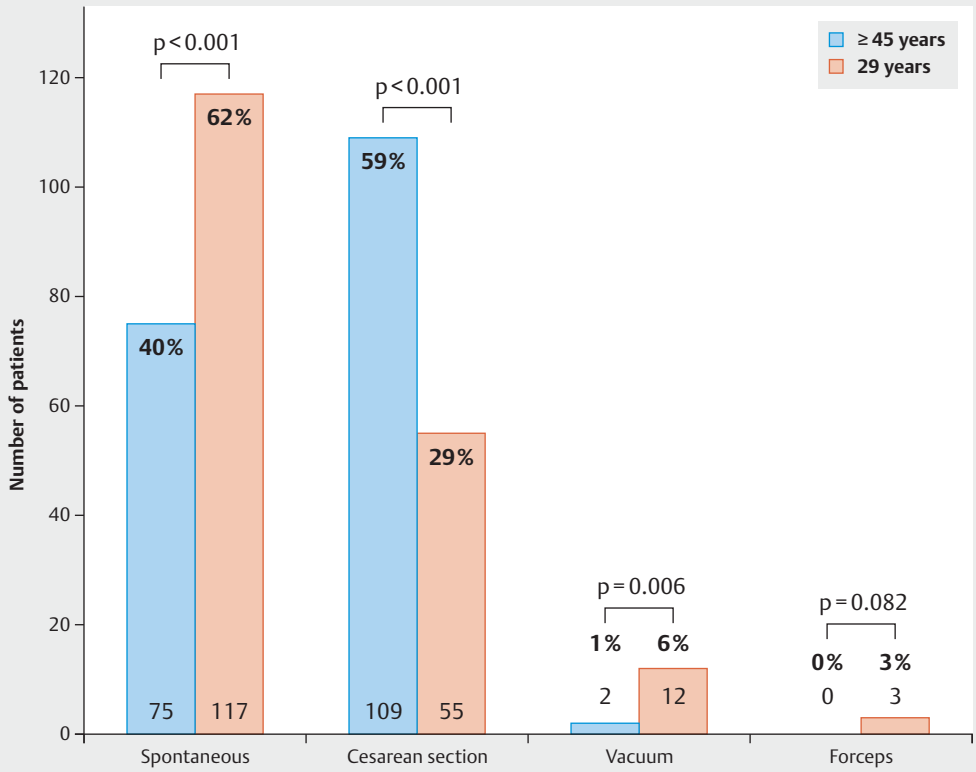
Descriptive statistics of the patient characteristics are given as mean ± standard deviation for continuous variables and as frequencies (%) for categorical data. N = 186 subjects aged ≥ 45 years were compared to a control group of women aged 29 years at the time of giving birth. Continuous variables were compared with the two-tailed Student's t-test. Frequencies were compared using the $\chi^2$-test or Fisher's exact test as appropriate. The level of significance was two-tailed at 0.05.

▶ **Table 2** Outcome variables such as delivery mode and fetomaternal complications for the study and control groups.

| | Study group (n = 186) | Control group (n = 186) | |
|---|---|---|---|
| Gestational age at delivery | 37 ± 4 | 39 ± 3 | **p < 0.001** |
| Fertility treatment | | | |
| ▪ IVF/ICSI | 63 (34%) | 6 (3%) | **p < 0.001** |
| ▪ Egg donation | 20 (32%) | 0 | **p < 0.001** |
| Delivery mode | | | |
| ▪ Spontaneous | 75 (40%) | 117# (62%) | **p < 0.001** |
| ▪ Cesarean section | 109 (59%) | 55 (29%) | **p < 0.001** |
| ▪ Vacuum extraction | 2 (1%) | 12# (6%) | **p = 0.006** |
| ▪ Forceps | 0 | 3 (3%) | p = 0.082 |
| Preterm delivery | 52 (28%) | 20 (11%) | **p < 0.001** |
| ▪ < 24 + 0 weeks | 2 | 1 | |
| ▪ 24 + 0–33 + 6 weeks | 30 | 8 | |
| ▪ 34 + 0–36 + 6 weeks | 20 | 11 | |
| Premature rupture of membranes | 18 | 3 | **p = 0.001** |
| Multiple pregnancy | 30 (16%) | 9 (5%) | **p < 0.001** |
| ▪ After IVF treatment | 24/30 (80%) | 4/9 (40%) | p = 0.085 |
| Fetal birth weight | 2 875 ± 908 g | 3 178 ± 740 g | **p = 0.001** |
| Blood loss | 459 ± 246 ml | 391 ± 258 ml | p = 0.558 |
| Preeclampsia | 14 | 5 | **p = 0.022** |
| Gestational diabetes | 23 | 4 | **p = 0.001** |
| HELLP syndrome | 3 | 0 | p = 0.248 |
| IUGR | 5 | 3 | p = 0.724 |

Descriptive statistics of the patient characteristics and outcome variables are given as mean ± standard deviation for continuous variables and as frequencies (%) for categorical data. Continuous variables were compared with the two-tailed Student's t-test. Frequencies were compared using the $\chi^2$-test or Fisher's exact test as appropriate. The level of significance was two-tailed at 0.05.

# A total of n = 187 births because in a twin pregnancy a vacuum extraction was performed for one twin with spontaneous delivery of the second twin.




▶ **Fig. 1** Mode of delivery with statistical analysis of differences between study and control group.

of 2.8 ± 2.1 previous births; 32% gave birth to their first child. Thirty-three (18%) women had had a cesarean section in an earlier pregnancy. Of this cohort, 63 (34%) had undergone in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI); 20 of them (32%) stated that they had used egg donation.

## Control group

All n = 186 women in the control group were 29 years of age. As shown in ▶ **Table 1**, the number of previous pregnancies was significantly lower in the control group. Gravidity ranged from 1 to 8 with a mean of 2.3 ± 1.5. Parity ranged from 0 to 7 with a mean of 1.8 ± 1.1 previous births; 50% gave birth to their first child. Twenty (11%) women had had a cesarean section in a previous pregnancy. The rate of assisted reproduction (IVF/ICSI) was significantly lower in the control group, with only 6 out of 186 women (3%) having had assisted reproduction ($p < 0.001$).

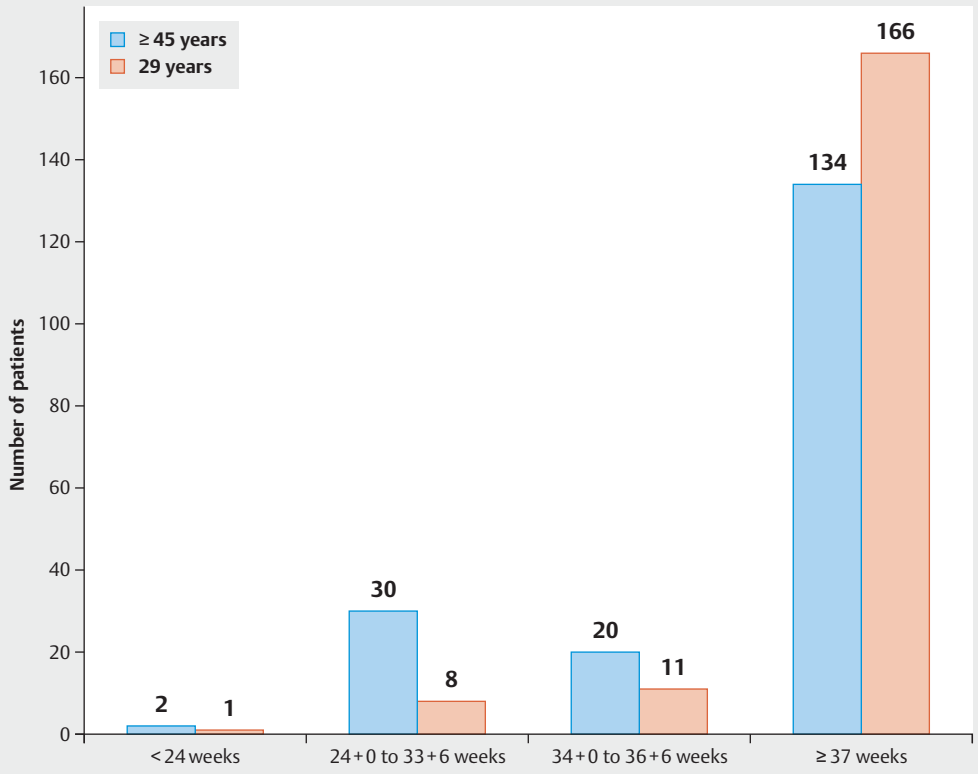
## Co-morbidities

A comparison of preexisting co-morbidities showed that the study group had higher rates of medical disorders such as hypertension (n = 13 vs. n = 0, $p < 0.001$), previous enucleation of uterine fibroids (n = 10 vs. n = 0, $p = 0.001$), previous breast cancer (n = 2 vs. n = 0, $p = 0.498$), infectious diseases such as hepatitis B (n = 4 vs. n = 1, $p = 0.371$) or HIV (n = 2 vs. n = 0, $p = 0.498$), depression (n = 2 vs. n = 1, $p = 1.000$) and epilepsy (n = 2 vs. n = 1, $p = 1.000$). The younger control group had more cases of preceding cervical conization (n = 4 vs. n = 3 in the study group, $p = 1.000$). There was an equal number of maternal cardiac arrhythmias (n = 3) in both groups. One 46-year-old woman had a myocardial infarction and stroke episode; one 29-year-old woman had a pulmonary embolism due to factor V Leiden mutation. Of the 13 women with preexisting hypertension, three had an IUGR and two developed preeclampsia.

## Delivery mode

As shown in ▶ **Fig. 1**, 75 (40%) women in the study group and 117 (62%) women in the control group delivered spontaneously ($p < 0.001$). Cesarean section was the most common mode of delivery in the study group, with an incidence of n = 109 (59%), and was performed significantly more often compared to the control group (n = 55 (29%), $p < 0.001$). The number of vacuum extractions was significantly lower in patients aged ≥ 45 years compared to the control group (n = 2 vs. n = 12, $p = 0.006$). Forceps extraction was not performed in the study group but was done in 3 women of the control group ($p = 0.082$).

We classified the cesarean sections according to the RCOG (Royal College of Obstetricians and Gynaecologists) guidelines and divided them into 4 groups: I Emergency (immediate threat




▶ **Fig. 2** Number of preterm deliveries in the study and control group.

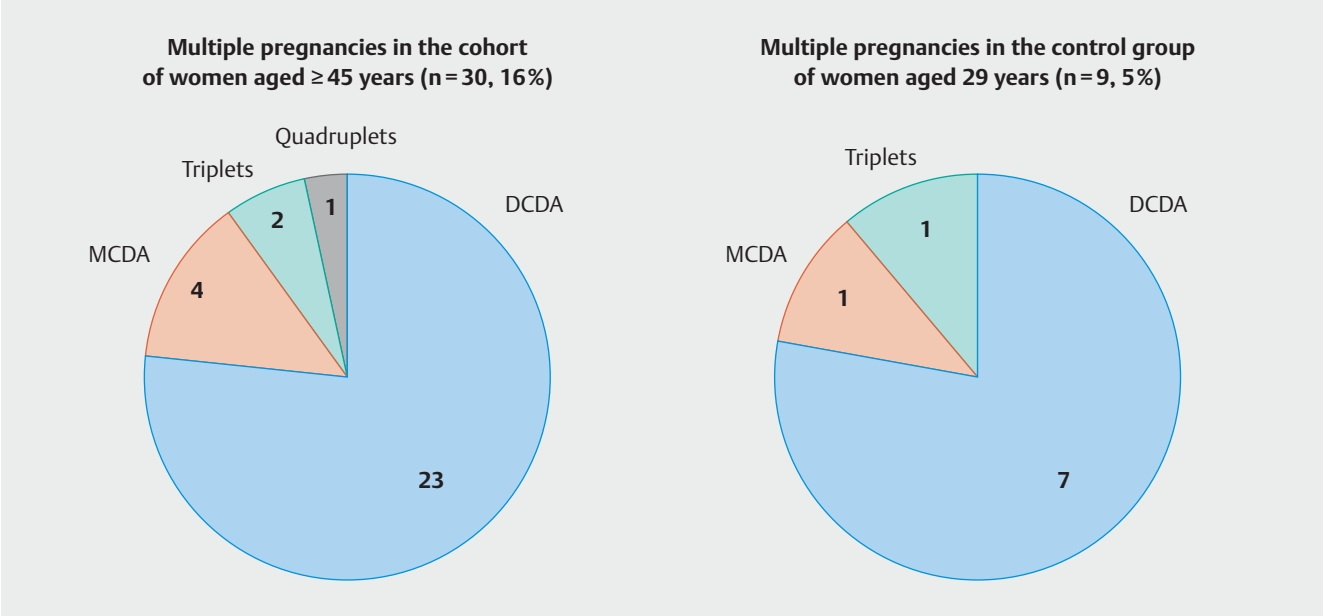
to life of woman or fetus, e.g. pathological CTG, preeclampsia, placental abruption); II Urgent (maternal or fetal compromise which is not immediately life-threatening, e.g. prolonged labor [for example, absence of further cervical dilation within 4 hours], early rupture of membranes and contractions); III Scheduled (needing early delivery but no maternal or fetal compromise, e.g. placenta previa, velamentous insertion); and IV Elective (at a time to suit the woman and maternity team, e.g. breech presentation, multiple pregnancies, previous cesarean section, maternal request). When sorted accorded to these classifications there were 37 (34%) Emergency, 24 (22%) Urgent, 3 (3%) Scheduled and 45 (41%) Elective cesarean sections in the study group. In the control group, 11 (20%) Emergency, 15 Urgent (27%), 2 Scheduled (4%) and 27 (49%) Elective cesarean sections were performed. These differences were not statistically significant. There was a comparable mean blood loss of 459 ± 246 ml in the study group and 391 ± 258 ml in the control group ($p = 0.558$). In both groups 7 (4%) patients had a blood loss ≥ 1000 ml. The mean birth weight was significantly lower in the study group, with 2875 ± 908 g in the study group vs. 3178 ± 740 g in the group of 29 year-olds ($p = 0.001$). The birth weight analysis for multiple pregnancies was averaged.

## Duration of pregnancy

As presented in ▶ **Table 2**, the mean gestational age of 37.1 ± 4.1 weeks at delivery of the study group was significantly lower compared to the control group with 38.6 ± 3.1 weeks ($p < 0.001$).

As shown in ▶ **Fig. 2**, in the advanced maternal age group there were 52 preterm deliveries (28%). Of these cases, 2 delivered at < 24 + 0 weeks (4%), 30 between 24 + 0 and 33 + 6 weeks (58%) and 20 gave birth between 34 + 0 and 36 + 6 weeks (38%). Twenty-two of these pregnancies were multiple pregnancies (42%). In contrast, the rate of preterm delivery was significantly lower in the control group (n = 52 vs. n = 20; $p < 0.001$). Only two preterm pregnancies were multiple gestations. One patient delivered at < 24 + 0 weeks, 8 between 24 + 0 and 33 + 6 weeks and 11 between 34 + 0 and 36 + 6 weeks.

Reasons associated with preterm delivery were cervical shortening of < 25 mm that was documented in 5 cases in the study group and in 3 cases in the control group ($p = 0.501$). In the study group, 8 patients had a cerclage compared to one patient in the control group ($p = 0.037$). Premature rupture of membranes occurred in 18 of the patients aged ≥ 45 years compared to 3 of the controls ($p = 0.001$), and chorioamnionitis was diagnosed in 4 vs. 3 subjects ($p = 1.00$). In the group of women who had early preterm deliveries of < 34 + 0 weeks, reasons for cesarean section included contractions in 7 women of the study group compared




▶ **Fig. 3** Distribution of multiple pregnancies in the cohort aged ≥ 45 years old and in the 29-year-old cohort.

to 5 in the control group, rupture of membranes (n = 9 vs. n = 1), pathological Doppler (n = 3 vs. n = 2) and preeclampsia (n = 7 vs. n = 0). Other indications were HELLP syndrome, growth restriction, twin reverse arterial perfusion, placental abruption and placenta previa. Of the 32 early preterm deliveries at < 34 + 0 weeks in the study group, 14 were multiple pregnancies compared to 1 out of 9 in the control group, with no difference in the cause of preterm delivery.

## Multiple gestations

There was a significantly higher rate of multiple pregnancies in the cohort aged ≥ 45 years compared to the cohort of 29-year-old women (p = 0.001). As shown in ▶ **Fig. 3**, 30 women in the study group (16%) had a multiple pregnancy; 23 of these were dichorionic diamniotic (DCDA) twins, 4 were monochorionic diamniotic (MCDA) twins, 2 were triplets and one gestation was a quadruplet pregnancy. In contrast, only 9 women (5%) of the 29-year-old cohort had multiple pregnancies; 7 of these were DCDA twins, one was a MCDA twin pregnancy and there was one case of a triplet pregnancy (p < 0.001). In the study group, 80% (24/30) of multiple pregnancies had had IVF compared to 40% (4/9) in the control group (p = 0.085). Two cases with dichorionic twins had electively undergone early selective reduction from a triplet pregnancy.

## Singleton pregnancies

There were 156 singleton pregnancies in the study group and 177 in the control group. There was a statistically higher rate of gravidity (4.4 ± 2.5 vs. 2.3 ± 1.5 [p < 0.001]), parity (2.9 ± 2.0 vs. 1.8 ± 1.1 [p < 0.001]) and IVF (n = 39 [25%] vs. n = 2 [1%] [p < 0.001]) in the study group compared to controls. The rate of cesarean sections was higher in the study group (n = 79 [51%] vs. n = 48 [27%], p < 0.001) compared to controls. In the study group, 75 women delivered spontaneously (48%), and 2 vacuum extractions were performed. In the control group of singletons, 115 (65%) women had a spontaneous delivery, 11 (6%) a vacuum delivery, and 3 (2%) a forceps delivery. Twenty-nine patients aged ≥ 45 years compared to 20 women in the younger cohort had had a previous cesarean section (p = 0.050). There was no significant difference in birth weight (3067 ± 819 vs. 3216 ± 720, p = 0.147) or duration of pregnancy (38 + 0 vs. 38 + 5 weeks, p = 0.054) and preeclampsia (8 preeclampsia, 1 HELLP in the study group vs. 5 preeclampsia, 0 HELLP in the control group, p = 0.311). Gestational diabetes was, however, significantly higher in the study group with singleton pregnancies (n = 20 vs. n = 4, p = 0.001).

## Complications

With a total of 14 cases of preeclampsia (defined as new onset of elevated blood pressure > 140/90 mmHg and proteinuria ≥ 0.3 g in a 24-hour urine collection) and 3 patients with HELLP syndrome in the study group, the incidence of these adverse outcomes was significantly higher compared to the control group with 5 cases of preeclampsia and no cases of HELLP syndrome (p = 0.022). The incidence of intrauterine growth restriction (IUGR) was comparable, with 5 pregnancies in the study group and 3 in the control group (p = 0.724). Severe adverse outcomes associated with placental dysfunction such as preterm placental abruption (n = 2 in the study group vs. n = 1 in the control group, p = 1.00) and intrauterine fetal death between 24 + 0 and 37 + 0 weeks (n = 2 in the study group vs. 1 in the control group, p = 1.00) did not differ significantly between the study cohorts. In the study group one neonate died 2 hours post partum (born at 20 + 5 weeks), one died after 10 days (born at 29 + 1 weeks) and one after 27 days (born at 25 + 2 weeks). In the control group one premature infant died im-

mediately post partum (born at 22 + 3 weeks), one died after nine hours (born at 24 + 0 weeks) and one after extubation on day 121 (born at 29 + 5 weeks). In the study group there was one case of trisomy 18, one case of trisomy 21 and one fetus with hydrocephalus. In the control group there was one case of transposition of the great arteries.

Placenta previa (n = 2 in the study group vs. n = 1 in the control group), velamentous cord insertion (1 vs. 0) and adherent placenta (0 vs. 1) only occurred in single cases and were not evaluated statistically.

The incidence of gestational diabetes (GDM) was significantly higher in women aged ≥ 45 years, with 18 women presenting with diet-controlled GDM and 5 women with insulin-dependent GDM compared to 4 cases with diet-controlled GDM in the control group (p = 0.001).

## Discussion

Improved fertility treatment options and a change in the sociocultural concept of family planning, especially in industrialized regions and big cities with a high availability of reproductive technologies, have led to increasing numbers of deliveries in women with advanced maternal age.

This study shows that the cesarean rate was significantly higher in women with advanced maternal age compared to a younger group of 29-year-old women. Luke et al. conducted a study of over 8 million live births in women aged 30–54 years and reported a significantly higher risk for prolonged and dysfunctional labor with increased maternal age [3], which is comparable to the high rate of urgent cesarean sections due to prolonged labor in women aged ≥ 45 years in our study. Greenberg et al. found similar delivery rates and proposed that myometrial contractility decreases with maternal age, but its function can be increased with uterotonics such as oxytocin and PGF2 alpha [14]. The hypothesis of decreased myometrial contractility is also supported by Elmes et al., who demonstrated the same results in experiments with rat uteri during labor [15]. Despite the age differences, in our study there was no difference in elective cesarean sections between groups (41 vs. 49 %).

The incidence of preterm deliveries, particularly early preterm deliveries, was higher in the study group of women with advanced maternal age for both singleton and multiple pregnancies, and birth weights were lower. There was a higher rate of multiple pregnancies in the study group, which is regarded as a risk factor for preterm delivery, premature rupture of membranes, and low birth weight and this could therefore indicate a bias. However, we hypothesized that the advanced maternal age was in itself a risk factor for preterm delivery. This is in contrast to the study by Dietl et al. which looked at 405 women over the age of 40 and found no significant differences in the rates of preterm delivery between different age groups. Dietl et al. concluded that the more frequent check-ups given to older women, the medical treatment of preexisting diseases, and delivery in a perinatal center resulted in comparable outcomes for different age groups [16].

In our study group there was not only an increased risk of an adverse outcome due to placental and endothelial dysfunction such as preeclampsia and HELLP syndrome but also an increased risk of gestational diabetes or premature rupture of membranes (PROM). One possible explanation for the higher rate of PROM could be the higher rate of multiple pregnancies with an associated risk of uterine distension; another hypothesis could be the higher rate of GDM in this cohort which could be correlated with an increased susceptibility to infection. One theory is that on a cellular level, cell death activates collagenase, a catabolic enzyme that can subsequently lead to instability of the membranes. The higher rate of gestational diabetes could be due to a higher rate of primary insulin resistance in older patients or previously undetected early-stage diabetes mellitus. The higher percentage of preeclampsia is possibly the result of a previously damaged endothelium or a sign of higher endothelial vulnerability in older patients, a hypothesis supported by the higher rate of preexisting hypertension in the advanced maternal age group. There were no maternal deaths in our study group of 186 cases. An international study by Laopaiboon et al. of 308 149 singleton pregnant women in 29 countries in Africa, Asia, Latin America, and the Middle East found significantly more adverse pregnancy outcomes, including maternal death and severe maternal outcomes in patients with an advanced maternal age of 35 years and older [6].

These outcomes are consistent with most findings in the literature although most studies analyzed women aged > 35 or 40 years. The impact on the medical, psychological, social and economic aspects of these late pregnancies should be taken into account. For instance, it is assumed that women of advanced maternal age tend to be more financially secure and have completed their vocational training, but the increased cost of conception, the increased rate of cesarean section and higher rates of perinatal maternal and fetal complications lead to increased healthcare costs [17]. Psychologically, pregnancies in older women can lead to higher scores in psychological distress tests, although few studies have analyzed this aspect [18].

It is possible that the rate of women who had fertility treatment in our study group, especially the rate of egg donation, could be underreported due to a feeling of shame or taboo. Similar to the rest of Europe, German health insurance companies do not bear the cost of fertility treatments in women above the age of 40 years, not just for medical and technical reasons but also from a social point of view [19]. Furthermore, egg donation is prohibited in Germany which leads to a high number of unreported egg donations performed abroad. In the annual report for 2014, the German IVF registry showed that the rate of clinical pregnancies per embryo transfer was 42 % in women aged < 24 years and decreased to 5.8 % in 45-year-old women and 4.19 % in women aged ≥ 46. The rate of miscarriages increased from 5 to 15 % in 25–35-year-old women to 40 % in women above the age of 45 [5]. Spandorfer et al. looked at the outcome of 288 IVF cycles using autologous oocytes in women aged ≥ 45 years and found a pregnancy rate of 21 % and a delivery rate of only 3 % [20]. These poor outcomes for fertility treatments in women of advanced maternal age should be made clear to affected women above the age of 40 before starting assisted reproduction.

Limitations of this study are a lack of data on race and body mass index. Detailed follow-up neonatal data is not included. The high number of IVF patients and multiple pregnancies may also constitute a bias. However, looking only at the singleton pregnancies, the rates of cesarean sections and gestational diabetes were still higher in the group aged ≥ 45 years. Despite the limitations, we were interested in this group of women primarily for their age and clinical outcomes as we wanted to identify relevant issues of care.

It is important to counsel patients about the risks any pregnancy at an advanced maternal age ≥ 45 years carries. This does not only include higher pregnancy risks such as preeclampsia, gestational diabetes, and preterm delivery that can result in severe maternal or fetal outcomes, but also higher numbers of complications during labor and a higher rate of cesarean sections. Women of advanced maternal age should be treated in a level I hospital to allow them and the fetus to be monitored closely at regular intervals. The possible role of fertility treatment – which is more common in older patients – as an independent risk factor should be examined in further studies with a higher sample size.

## Conflict of Interest

The authors declare that they have no competing interests.

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