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GENERAL GYNECOLOGY

Caesarean section and its impact on fertility and time to a subsequent pregnancy in Germany: a database analysis in gynecological practices

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Abstract
Purpose To analyze the impact of caesarean section (CS) on fertility and time to pregnancy in German gynecological practices.
Methods Women initially diagnosed for the first time with a vaginal delivery (VD) or CS between 2000 and 2013 were identified by 227 gynecologists in the IMS Disease Analyzer database. They were included if they were aged between 16 and 40 years, and were not previously diagnosed with female sterility. The two main outcomes were the first-time diagnosis of female sterility and the time between the first delivery and the next pregnancy within 10 years. A multivariate Cox regression model was used to predict these outcomes on the basis of patient characteristics.
Results 6483 patients were included in the CS group and 6483 in the VD group. Mean age was 30.6 years and the proportion of individuals with private health insurance amounted to 9.0 %. Within 10 years of the index date, 19.5 % of women who delivered by CS and 18.3 % of women who delivered vaginally were diagnosed with sterility (p value = 0.0148). CS and polycystic ovary syndrome significantly increased the risk of sterility. Within 10 years of the index date, 57.9 % of women who underwent a CS and 64.0 % of women who delivered vaginally were pregnant for the second time (p value <0.001). CS, polycystic ovary syndrome, and the deterioration of menstrual cycle significantly decreased the chance of becoming pregnant a second time.
Conclusions CS is associated with an increased risk of sterility and a decreased number of subsequent pregnancies in Germany.

Keywords Caesarean section · Complications · Fertility · Subsequent pregnancies

Introduction

Each year, more than 135 million women worldwide give birth, resulting in approximately five births per second [1]. In 2008, caesarean sections (CSs) were used in more than 15 % of the deliveries in 50 % of the countries [2]. Initially developed to protect both mother and child, i.e., to indirectly reduce the pregnancy-related risk of death, CS has been paradoxically associated with major complications, such as infection, blood loss, and others for the mother, as well as injury and vital breathing problems for the baby [3–5]. These CS-associated complications may occur during the same pregnancy but also afterward [5]. It was demonstrated that women who underwent CS were at a higher risk for malpresentation, placenta previa, antepartum hemorrhage, placenta accreta, prolonged labor, emergency caesarean, uterine rupture, preterm birth, low birth weight, and infants who were small for their gestational age [6].

Although numerous studies indicated that CS is responsible for major maternal health problems, its impact on fertility remains under debate. Indeed, a recent work

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based on more than one million deliveries revealed that the impact of CS on the subsequent birth rate is weak and not statistically significant in young women [7]. These findings were very new, since many previous works had supported the opposing stance that CS is an important risk factor for maternal sterility [8–12].

Since all of these studies used different populations and various methods, the question concerning the risk of caesarean section remains current. Therefore, the goal of our study was to analyze the impact of caesarean section on fertility and time to next pregnancy using existing data from German gynecological practices.

Methods

Database

The Disease Analyzer database (IMS Health) compiles drug prescriptions, diagnoses, basic medical and demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners [13]. Diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical (ATC) Classification System) and the quality of reported data have been monitored by IMS based on a number of criteria (e.g., completeness of documentation, linkage between diagnoses and prescriptions).

In Germany, the sampling methods used for the selection of physicians' practices were appropriate for obtaining a representative database of general and gynecological practices [13]. Prescription statistics for several drugs were very similar to data available from pharmaceutical prescription reports [13]. The age groups for given diagnoses in Disease Analyzer were also commensurate with those in corresponding disease registries [13].

Study population

First-time documentations of full-term natural birth (NB, ICD 10: O80) or CS (ICD 10: O82) from January 2000 until December 2013 were defined as the index dates; the latest follow-up date was identified as April 2015. Further inclusion criteria comprised age of between 16 and 40 years at the index date and no diagnosis of female infertility (ICD 10: N97) or procreative management (ICD 10: Z31) prior to index date. A total of 10,990 women with NB and 6692 women with CS were available for persistence analysis. These patients were observed in 227 gynecological practices. Finally, 6483 women with CS and 6483 women with NB were chosen after individual matching (1:1) based on age, type of health insurance (private or statutory) [14], and diagnosis of obesity (ICD 10: E66).

Study outcome

The primary outcome measure was the first-time diagnosis of female sterility (ICD: N97) after the index pregnancy, whereas the second outcome parameter was the time difference between the first delivery and the next pregnancy (all pregnancies had been included, irrespective of outcome).

Covariates

Demographic data included age and type of health insurance (private or statutory). Co-diagnoses were determined based on primary care diagnoses (ICD-10 codes) for deterioration of menstrual cycle (N92), endometriosis (N80), polycystic ovary syndrome (E28.2), diabetes mellitus (E10, E11, E14) or elevated blood glucose level (R73), chlamydial infection (A74.9), and depression (F32, F33).

Statistical analysis

Descriptive statistics were provided, and differences in characteristics of patients (NB versus CS) were assessed using paired *t* tests, Wilcoxon tests for paired samples, or McNemar's tests.

The cumulative incidence of a sterility diagnosis was exhibited for up to 10 years after index date using Kaplan–Meier curves. Log-rank tests were used to compare women with NB versus women with CS with regard to incident sterility diagnosis. Cox proportional hazards models (dependent variable: sterility) were used to estimate the effect of CS and to adjust for confounders. The Cox regression method was used to investigate the effect of several variables on the time a specified event takes to occur.

The time that had elapsed from first delivery documentation until the proof of pregnancy was also assessed by applying Kaplan–Meier curves. Cox regressions were used to determine the influence of CS with regard to improving or impairing the chances of a subsequent pregnancy. A p value <0.05 was considered statistically significant. All calculations were carried out using SAS 9.3 (SAS Institute, Cary, USA).

Results

Patient characteristics

Patient characteristics are illustrated in Table 1. A total of 6483 and 6483 patients were included in the NB and the CS groups, respectively. Mean age was 30.6 years (SD = 5.2 years) and the proportion of individuals with

private health insurance amounted to 9.0 % in both groups, although there was no difference in terms of obesity, deterioration of menstrual cycle, polycystic ovary syndrome, depression, and chlamydial infections between the two groups. Women with endometriosis and diabetes (or elevated blood glucose level) were more likely found in the group receiving CS compared to the group delivering vaginally (2.1 versus 1.4 %, p value = 0.0046; and 2.3 versus 1.7 %, p value = 0.0212).

Caesarean section and sterility diagnosis

Figure 1 displays cumulative incidence curves of sterility diagnosis in women with prior VD and CS in gynecological practices. Within 10 years of the index date, 19.5 % of CS patients and 18.3 % of NB patients were diagnosed with sterility (log-rank p value = 0.0148). In women with sterility diagnosis, the median time to the first sterility diagnosis was 807 days in the CS group and 904 days in the NB group (p = 0.020). The results of the Cox regression model are shown in Table 2. CS and polycystic ovary syndrome significantly increased the risk of sterility (OR = 1.17, 95 % CI 1.05–1.32 and p value = 0.0066; OR = 1.26, 95 % CI 1.01–1.57 and p value = 0.0470, respectively).

Caesarean section and time to second pregnancy

Figure 2 displays cumulative incidence curves of second pregnancy in women with prior VD and CS in gynecological practices. Within 10 years of the index date, 57.9 % of CS women and 64.0 % of NB women were pregnant for the second time (log-rank p value <0.001). The median time till the second pregnancy was 2198 days in CS and 1743 days in NB women ($p < 0.001$). The results of the Cox regression model are shown in Table 3. CS, polycystic ovary syndrome and the deterioration of menstrual cycle significantly decreased the chance of becoming pregnant for the second time (OR = 0.89, 95 % CI 0.85–0.95; OR = 0.76, 95 % CI 0.67–0.87; and OR = 0.65, 95 % CI 0.57–0.76, respectively, all p values lower than 0.0001).

Table 1 Baseline characteristics of patients with vaginal delivery (VD) or caesarean section (CS)

Variables	VD	CS	p value
Number of patients	6483	6483	
Age in years (mean ± standard deviation)	30.6 (5.2)	30.6 (5.2)	1.000
Private health insurance (%)	9.0	9.0	1.000
Diagnoses prior to index date (%)			
Obesity (E66)	7.7	7.7	1.000
Deterioration of menstrual cycle (N92)	5.3	5.7	0.3156
Endometriosis (N80)	1.4	2.1	0.0046
Polycystic ovary syndrome (E28.2)	5.9	6.6	0.0756
Diabetes mellitus (E10, E11, E14) or elevated blood glucose level (R73)	1.7	2.3	0.0212
Depression (F32, F33)	4.7	4.3	0.1889
Chlamydial infection (A74.9)	1.9	2.1	0.2595

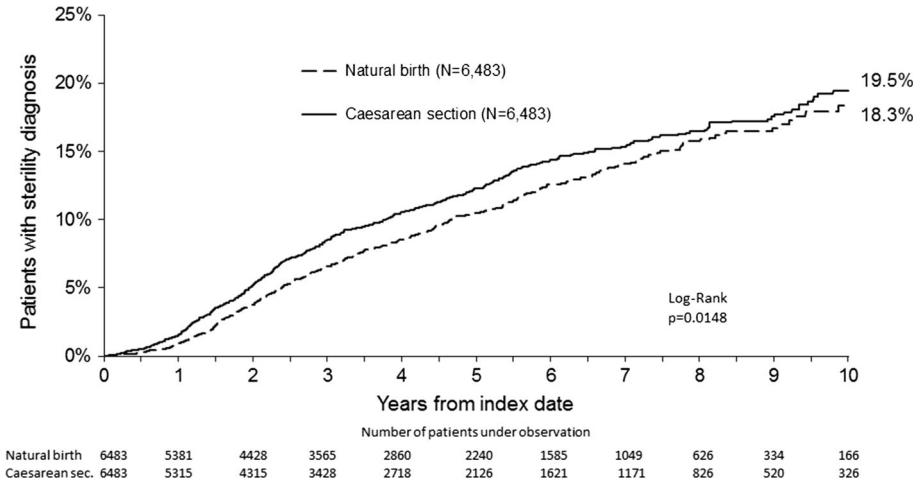

Fig. 1 Cumulative incidence of sterility diagnoses in women with prior vaginal delivery and caesarean section in gynecological practices

Discussion

In this study, we discovered that CS increased the risk of sterility and decreased the chance of a second pregnancy. Interestingly, polycystic ovary syndrome also impacted these two outcomes, whereas the deterioration of menstrual cycle only decreased the probability of a future pregnancy.

The association between a previous CS and sterility has been controversially discussed in the literature. The potential negative effects of CS on subsequent pregnancies are of particular importance, since the incidence of CS has increased in the past decades [15]. In 2003, Porter and colleagues addressed this issue with a review of the main studies performed between the 1980s and the 2000s [10]. Based on a Scandinavian survey comprising 812 women, Hemminki et al. determined that women who had had a CS exhibited lower fertility compared to women who delivered vaginally [8]. Another study showed that only 47 % of the women delivering by CS were pregnant again within the following 5 years, whereas more than 60 % of the women with an operative vaginal delivery were subsequently pregnant again [9]. In 2013, a meta-analysis including 18 studies from America and Europe which were conducted up to 2006, corroborated the findings of the study conducted by Porter et al. [10, 15]. Indeed, it was stated that women who delivered by CS had a 9 % lower subsequent pregnancy rate (RR = 0.91, 95 % CI 0.87–0.95) and 11 % lower birth rate (RR = 0.89, 95 % CI 0.87–0.92), compared with patients who had delivered vaginally [15]. Nonetheless, several of the studies included in the meta-analysis did not control for maternal age and did not specifically analyze primary elective CS, artificially resulting in stronger CS effects on sterility. Since few authors were concerned about these potential biases, Gurol-Urgancy and colleagues retrospectively studied 1,047,644 deliveries in 2014 and revealed that the impact on the subsequent birth rate was weak (HR = 0.96, 95 % CI 0.94–0.98) when only taking Caesarean for breech into consideration and that it was not statistically significant in women under the age of 30 (HR = 0.98, 95 % CI 0.96–1.01) [7]. By contrast, the impact of the Caesarean delivery was stronger for other indications (HR = 0.81, 95 % CI 0.78–0.83) and in case of emergency CS

Table 2 Association between caesarean section and sterility

Variables[a]	Hazard ratio[b] (95 % CI)	*p* value
Caesarean section	1.17 (1.05–1.32)	0.0066
Polycystic ovary syndrome	1.26 (1.01–1.57)	0.0470

[a] Stepwise selection of variables: only variables with significant effect are shown

[b] Adjusted for deterioration of menstrual cycle, endometriosis, polycystic ovary syndrome, diabetes mellitus, depression and chlamydial infection

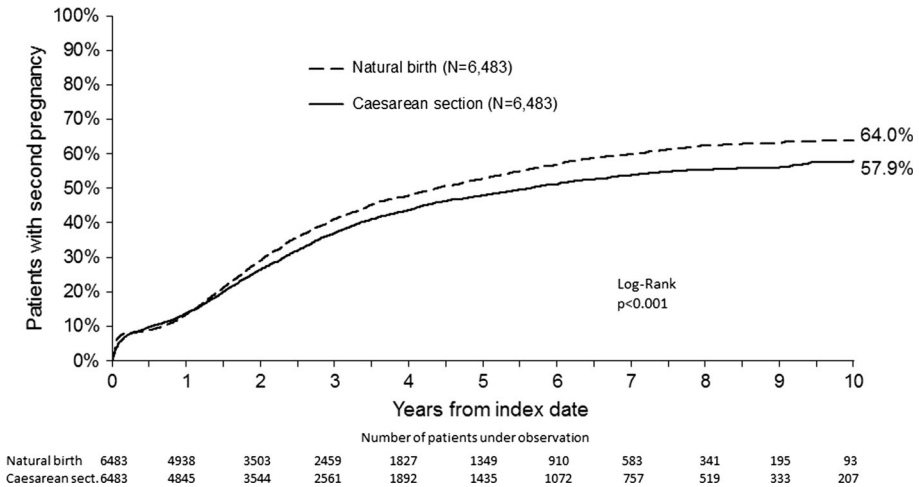

Fig. 2 Cumulative incidence of second pregnancy in women with prior vaginal delivery and caesarean section in gynecological practices

Table 3 Association between caesarean section and time to second pregnancy

Variables[a]	Hazard ratio[b] (95 % CI)	*p* value
Caesarean section	0.89 (0.85–0.95)	<0.0001
Polycystic ovary syndrome	0.76 (0.67–0.87)	<0.0001
Deterioration of menstrual cycle	0.65 (0.57–0.76)	<0.0001

[a] Stepwise selection of variables: only variables with significant effect are shown

[b] Adjusted for deterioration of menstrual cycle, endometriosis, polycystic ovary syndrome, diabetes mellitus, depression and chlamydial infection

(HR = 0.91, 95 % CI 0.90–0.93) [7]. Interestingly, the authors also found that ethnicity (black: HR = 0.85, 95 % CI 0.81–0.90), age (35–40 years: HR = 0.63, 95 % CI 0.60–0.67) and deprivation (Q4 quintile: HR = 0.81, 95 % CI 0.79–0.84) had a greater effect on fertility [7], substantiating the hypothesis of potential biases in previous studies. Despite the fact that this last study has resulted in important findings demonstrating that the association between CS and sterility should be very cautiously given credence, one must bear in mind that this work displays important limitations. Firstly, all women analyzed in this study originated from maternity units in England, thus potentially betraying a geographical bias, a population bias or even a bias in the collection of the data. Secondly, these findings have not yet been corroborated, and many authors remain convinced regarding the deleterious effects of CS on sterility.

Several hypotheses could explain the close correlation between CS and sterility [10, 15–17]. It may be of importance to consider that this association is bidirectional. CS appears to be a potential cause of sterility, although maternal history of subfertility is an indication for CS [18–20]. In 2002, Murphy and colleagues suggested that infection, adhesion formation and placental bed disruption related to CS may increase the risk of sterility [16]. Other authors have also raised the theory that emergency CS has deleterious psychological repercussions on women, thus interfering with their disposition for a second pregnancy [10, 17]. Finally, if there is an association between CS and sterility, it is clear that CS increased the delay of the second pregnancy. In 2013, O'Neill and colleagues reviewed 11 articles including a total of 750,407 women, and their studies indicated that there was an increased waiting time to the next pregnancy and risk of subfertility among women with CS [21].

Our data are in agreement with this literature, since we demonstrated that CS increased the risk of sterility and decreased the chance of a second pregnancy. Moreover, we also indicated that polycystic ovary syndrome, a heterogeneous endocrine disorder, increased the risk of sterility and decreased the chance of a second pregnancy, as has been reported previously [22]. Finally, we showed that the deterioration of the menstrual cycle—which may or may not be associated with CS—and polycystic ovary syndrome delayed the occurrence of second pregnancy.

Retrospective primary care database analyses are generally limited by the validity and completeness of the data on which they are based. The present study included several limitations, such as the assessment of sterility, and the definition of CS use and co-morbidities, which relied solely on ICD codes entered by primary care physicians. Furthermore, data pertaining to socioeconomic status (e.g., education, income) and lifestyle-related risk factors (e.g., smoking, alcohol, physical activity) were also lacking. An additional limitation we would like to acknowledge is that no information was available regarding the desire of the respective subjects for a subsequent pregnancy. We assumed that this desire was not considerably different between the two groups. Furthermore, no information was available about the indications for the respective CS. These indications could account for the difference in the outcomes. Moreover, our database did not allow us to separate elective Caesarean for breech, Caesarean for other indications, and emergency Caesarean. There was also no information about the assisted reproductive technology (ART) use. There was only an indirect code which indicated counseling for ART but there was no data on its actual use, the type of treatment and the number of treatment cycles. Since no reliable information was obtained with this code, we did not include it in the analysis.

The study also has several strengths. More than 12,000 German women were included in this study. Furthermore, we used precise inclusion criteria and selected a high number of gynecological practices. Finally, the Disease Analyzer database (IMS Health) is well documented, allowing a clear definition of CS and VD in agreement with the ICD-10 classification. Thus, our results can be generalized and extended to women currently followed in German gynecological practices and who are not diagnosed with female sterility.

Overall, the present study indicates that CS in Germany is associated with a slightly increased risk of sterility and a decreased chance of a second pregnancy. This might be more pronounced in certain subgroups and warrants further research. If these findings are substantiated by other studies, there may be a need for intensive management and follow-up for women who have undergone a CS in the past in order to prevent deleterious effects of this delivery on future pregnancies.

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Compliance with ethical standards

Conflict of interest LJ, VZ, IS, KW, KK and GM have no conflict of interest.

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