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Is the incidence of recurrent pregnancy loss increasing? A retrospective register-based study in Sweden

EMMA RASMARK ROEPKE[1], LEIF MATTHIESEN[2], REBECCA RYLANCE[3] & OLE BJARNE CHRISTIANSEN[4,5]

[1]Department of Obstetrics and Gynecology, Skåne University Hospital, Lund University, Malmö, [2]Department of Obstetrics and Gynecology, Helsingborg Hospital, Affiliated Lund University, Helsingborg, [3]Department of Research and Development, Skåne University Hospital, Lund, Sweden, [4]Fertility Clinic 4071, University Hospital Rigshospitalet, Copenhagen, Denmark, and [5]Department of Obstetrics and Gynecology, Aalborg University Hospital, Clinical Institute at Aalborg University, Aalborg, Denmark

Key words
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Correspondence
Emma Rasmark Roepke, Skåne University Hospital, Jan Waldenströmsgatan 47, 205 02 Malmö, Sweden.
E-mail: emma_36@hotmail.com

Conflict of interest
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Abstract

Introduction. The aim of this study was to estimate the incidence of recurrent pregnancy loss (RPL). The prevalence of RPL defined as three or more consecutive miscarriages before gestation week 22, is often stated to be 1%. To our knowledge no study has estimated the incidence of RPL, which might be more informative and clinically relevant than the prevalence. *Material and methods.* This retrospective register-based study was conducted from 2003 until 2012 in Sweden with data provided by the Swedish National Board of Health and Welfare. In all, 6852 women were registered with the diagnoses of RPL in the National Patient Register. The incidence of RPL is the number of new women receiving the RPL diagnosis per year in the numerator and population at risk in the denominator. *Results.* For each year, from 2003 to 2012, the incidence was calculated in two different risk populations: [1] all women aged 18–42 years, and [2] all women registered as being pregnant (deliveries or miscarriages). The average incidence in the study period was 53 per 100 000 (0.05%) in women aged 18–42 years and 650 per 100 000 (0.65%) in women who had achieved pregnancy in the period. The incidence of RPL in the two risk populations increased by 74 and 58%, respectively, during the study period. *Conclusion.* This study suggests that the incidence of RPL increased during the 10-year period studied. Causes can only be speculated upon in this study design, but might be associated with environmental changes, as the increase was fairly rapid.

Abbreviations: ART, assisted reproductive technology; NBHW, National Board of Health and Welfare; NPR, National Patient Register; RPL, recurrent pregnancy loss.

Introduction

Epidemiological studies of recurrent pregnancy loss (RPL) are important to gain an understanding of the disorder and its occurrence in the population. The incidence of RPL is the number of new women each year suffering their third consecutive pregnancy loss in a population at

Key message

In Sweden the incidence of recurrent pregnancy loss increased during a 10-year period, 2003–2012. The incidence of recurrent pregnancy loss increased by 74% in the population of women aged 18–42 years and by 58% in the population of pregnant women.

risk. Incidences can be used to compare the risk of RPL between different populations or in subgroups in the same population, and to compare changes over time, the latter being important for identifying risk factors [1]. Estimation of the incidence of RPL is helpful for planning clinical investigations and treatment protocols or for cost-benefit calculations for allocating resources for reproductive care.

Although the incidence is mentioned in many studies, they are probably actually referring to prevalence, as these two terms are often used incorrectly as synonyms. The prevalence of RPL is the number of all women in a population who, at a specific time point, have had three or more consecutive miscarriages. Many studies state that RPL occurs in 1% of women, referring to Stirrat [2]. Other studies have reported frequencies of RPL of between 0.5% and 2.3% [1–6]. The above studies actually report the prevalence rather than the incidence of RPL.

One major obstacle to estimating the incidence, is the lack of consensus on whether two or three miscarriages are required for a classification of RPL [1,7–12]. In this study, we define RPL as three or more consecutive clinically diagnosed miscarriages, before gestational week 22 [2,6,13,14]. Another obstacle is preclinical miscarriages, where the miscarriage is not included in any register. Regarding defining the population at risk of experiencing RPL, which is the denominator in the calculation of the incidence, there is huge diversity in the literature. A risk population could in theory be women trying to conceive [5,13–16], women with pregnancy [17], all women in the population [12,18], women who have attempted pregnancy a minimum of two or three times [19] or fertile women [6]. In this study, we have chosen all women registered with a pregnancy and women between 18 and 42 years (fertile age) as two risk populations.

The *primary aim* of this study was to estimate the incidence of the diagnosis RPL in the National Patient Register (NPR) in Sweden over 10 years from 2003 to 2012. The *second aim* was to estimate how many women had three or more consecutive miscarriages during that period, without being diagnosed with RPL in the NPR. This group can indicate whether RPL is under-diagnosed. The *third aim* was to estimate the proportions of primary and secondary RPL.

Material and methods

Study design

This retrospective register-based study of women with RPL was based on data from 2003 to 2012 from the NPR provided by the National Board of Health and Welfare (NBHW) in Sweden. Reporting information to the register, for example diagnosis codes, is mandatory and delivered to the NBHW once a month from each of the 21 county councils in Sweden. Since 1987, the NPR has included all in-patient care in Sweden, and since 2001 the register has also covered outpatient visits, including both private and public caregivers. The underreporting of inpatient data has been estimated to be less than 1%. The rate of underreporting for outpatients is not stated [20]. The Medical Birth Register, also provided by the NBHW, was used for information about the parity of the women in the study.

Study population

The definition of RPL used in this study was three or more consecutive miscarriages before gestational week 22. RPL was defined according to the 10th version of the International Classification of Diseases as RPL with or without an ongoing pregnancy, codes O26.2 and N96.9, respectively.

The incidence of RPL, defined as the number of new women each year suffering their third consecutive pregnancy loss in a population at risk, was estimated for each year in the period 2003–2012. A new case of RPL was counted in the year a woman was registered with a code of O26.2 or N96.9 for the first time. The patients diagnosed with RPL in the whole study period are called study group A.

As we had chosen two risk populations, two incidences of RPL were estimated. The first incidence was estimated among women between 18 and 42 years of age who were found in the Statistics Sweden database [21]. This incidence was calculated as the number of new women with RPL per year/women aged 18–42 years per year in the study period. The second incidence was estimated among women who were pregnant, which was defined as a delivery or a miscarriage included in the NPR for each year in our defined period.

Data were provided by the NBHW. This incidence was calculated as the number of new women with RPL per year/women with delivery or miscarriage in the same year in the studied period. A mean for each of the two incidences of RPL over the 10-year period was also estimated (Table 1).

Our second outcome was an estimate of how many women between 18 and 42 years of age, with three or more consecutive miscarriages in the register were left without the diagnosis RPL (O26.2, N96.9) in the NPR. This group comprised women without an RPL diagnosis in the register who, between 2003 and 2012, had three or more of the following ICD codes (main or bi-diagnosis) without interspersed live births: O02.1, O03 (including sub-diagnosis O03.0-O03.9). This study group was called B. In this study group, at least 90 days were required between two registered diagnoses of miscarriage to count as a new miscarriage, since the same diagnoses can be

used several times in different contacts within the healthcare system (Figure 1). The 90 days was defined by the authors from a clinical discussion of how long the clinical course of a miscarriage can last with a risk of several admissions for the same miscarriage.

To identify patients with primary and secondary RPL, patients identified in the NPR as study groups A and B were matched in the Medical Birth Register for their parity history. Primary RPL is the occurrence exclusively of miscarriages, whereas secondary RPL is defined as three consecutive miscarriages following a prior delivery. To identify primary and secondary RPL in study group A, the date of the first diagnosis with RPL (O26.2 or N96.9) was compared with the date of a possible delivery. In study group B the date of the third registered miscarriage was compared with the date of registered birth (Figure 1). To calculate the incidence of primary and secondary RPL, the number of patients with primary and secondary RPL in both study groups were divided, separately, by the total number of patients in study groups A+B.

Statistical analyses

We calculated an incidence proportion: "number of new cases of a disease per year"/"population at start of the period", although we were not able to obtain data on the

Table 1. Descriptive data on study population and risk population. Data on age-distribution of the study population; women with recurrent pregnancy loss. The number of new women with three or more consecutive miscarriages each year in the study period, 2003–2012. Two risk populations, women with pregnancy and women aged 18–42 years, are presented annually. The incidence for each risk population is shown for recurrent pregnancy loss per year studied.

Year	Group A[a]	Group B[b]	Group A + B	Mean age (years)	Women aged 18–42 years	Women with miscarriage or delivery	Incidence per 100 000 women age 18–42 years (%)	Incidence per 100 000 pregnant women (%)
2003	599	9	608	32.9	1 431 628	109 889	42 (0.042)	553 (0.55)
2004	524	50	574	33.1	1 436 069	111 922	40 (0.040)	513 (0.51)
2005	512	84	596	33.6	1 440 289	111 402	41 (0.041)	535 (0.54)
2006	473	94	567	33.4	1 450 924	118 523	39 (0.039)	478 (0.48)
2007	606	94	700	33.0	1 458 554	119 166	48 (0.048)	587 (0.59)
2008	724	117	841	33.3	1 472 715	121 516	57 (0.057)	692 (0.69)
2009	723	129	852	33.0	1 488 481	122 711	57 (0.057)	694 (0.69)
2010	829	121	950	33.2	1 500 865	126 187	63 (0.063)	753 (0.75)
2011	894	142	1036	33.1	1 511 549	125 938	69 (0.069)	823 (0.82)
2012	968	150	1118	33.2	1 524 130	127 781	73 (0.073)	875 (0.88)
Total	6852	990	7842					

[a]Group A: Women registered with the diagnosis code of RPL (O26.6, N96.9).
[b]Group B: Women with three or more consecutive miscarriages without registered diagnosis of recurrent pregnancy loss.

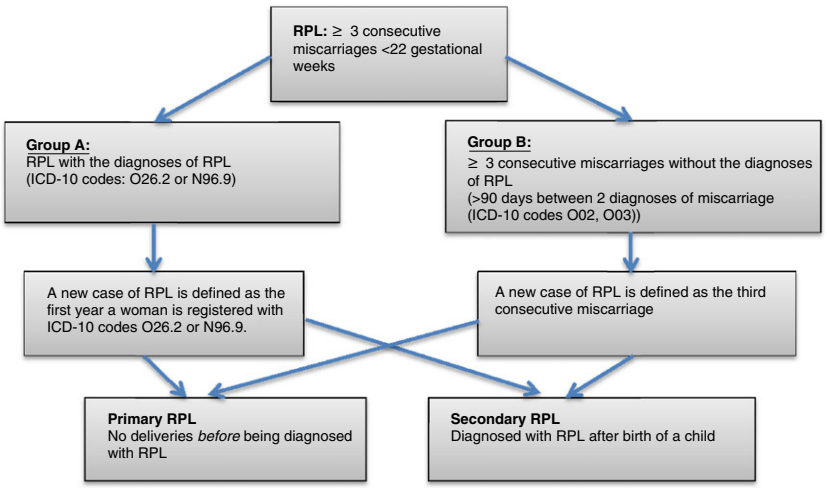

Figure 1. Women with three or more consecutive miscarriages divided into two study groups, A and B, with or without a registered diagnosis code. RPL, recurrent pregnancy loss. [Color figure can be viewed at wileyonlinelibrary.com].

population at the start of each year, only for the total year. Descriptive statistics were presented and the incidence proportion calculated. Differences in incidence proportions over time were tested with a two-tailed Z-test for two populations, which is used to analyze whether two populations differ significantly in some characteristics, for example incidence. When comparing our two incidence proportions in two time periods, our null hypothesis was: the two incidence proportions in the two time periods are equal. To test the hypothesis, the test statistic Z was calculated by dividing the estimated incidence difference by its standard error. The Z-value was compared with critical values of the test statistic at a 0.05 significance level.

Data management and statistical analyses were performed with SAS (SAS Institute, Cary, NC, USA) and IBM SPSS STATISTICS Version 23 for Mac (IBM Corp., Armonk, NY, USA).

Ethical approval

Recruited patients were anonymous, with personal identification numbers not revealed in the received data. Consequently, informed consent was not obtained. The study was approved by the ethics committee of Lund, on 9 January 2014, with protocol number 2014/1.

Results

Study group A included 6852 women and study group B 990 women. The total number of women with RPL during the 10-year period was thus 7842.

Incidence of RPL

The two annual incidences of RPL for the different risk populations are shown in Figures 2 and 3. The mean incidence of RPL in the 10-year period for women aged 18–42 years was 53/100 000 women, or 0.053%. The lowest and highest incidence for women between 18 and 42 years suffering their third consecutive miscarriage in the 10-year period was 39 and 73/100 000 women. Regarding pregnant women, the mean incidence was estimated to be 650/100 000 women, or 0.65%, with the lowest and highest incidences at 478 and 875/100 000 pregnant women.

Incidence over time

Comparing the period 2003–2007 with the period 2008–2012 there was an increasing proportion of incidences over time. The periods were tested with a two-tailed *Z*-test for two populations. The differences in the incidence in the two time periods for women aged 18–42 years and pregnant women were statistically significant: $Z = 18.1$ ($p < 0.0001$) and $Z = 15.9$ ($p < 0.0001$), respectively. For women aged 18–42 years, there was a 74% relative increase in the incidence of RPL during the 10 years studied. The relative increase for pregnant women was 58%.

Women without the diagnosis RPL in NPR

We found that 990 of the total 7842 (12.6%) women with three or more miscarriages in the NPR were not diagnosed with RPL over the 10-year period.

Primary and secondary RPL

The proportion of primary RPL and secondary RPL was 51.4% (4027/7842) and 48.6% (3815/7842), respectively.

Of the 7842 women with RPL, 4901 (62.5%) had given birth after the diagnosis of RPL, and 1472 patients (18.8%) had never given birth at the end of the studied period.

Discussion

The main results of this study were that the mean incidence of RPL during 2003 and 2012 was 53/100 000 in women aged 18–42 years and 650/100 000 in women who were pregnant. A 74% and 58% increase, respectively, in the incidence of RPL in women aged 18–42 years and pregnant women was found during the 10 years.

The main strength of this study is that, to our knowledge, it is the first register-based study estimating the population incidence of RPL. We used the definition of RPL endorsed by the European Society of Human Reproduction and Embryology and the Royal College of Obstetricians and Gynaecologists [6,22]. Risk populations for the denominator were chosen by the authors. Other potential risk populations could be all women irrespective of age but would comprise women with ages outside the fertile period, not at risk for the disorder. Women with a history of at least three pregnancies could also be a chosen risk population, although probably enriched by women with RPL trying to compensate for their previous pregnancy loss by attempting further pregnancies.

In our study, physicians made the diagnoses of miscarriage and RPL, which was a strength compared to self-reported miscarriages. In previous studies of RPL, prevalence has been based on questionnaires completed by the patients, with the known methodological problems of potential recall and selection bias [3,4,23].

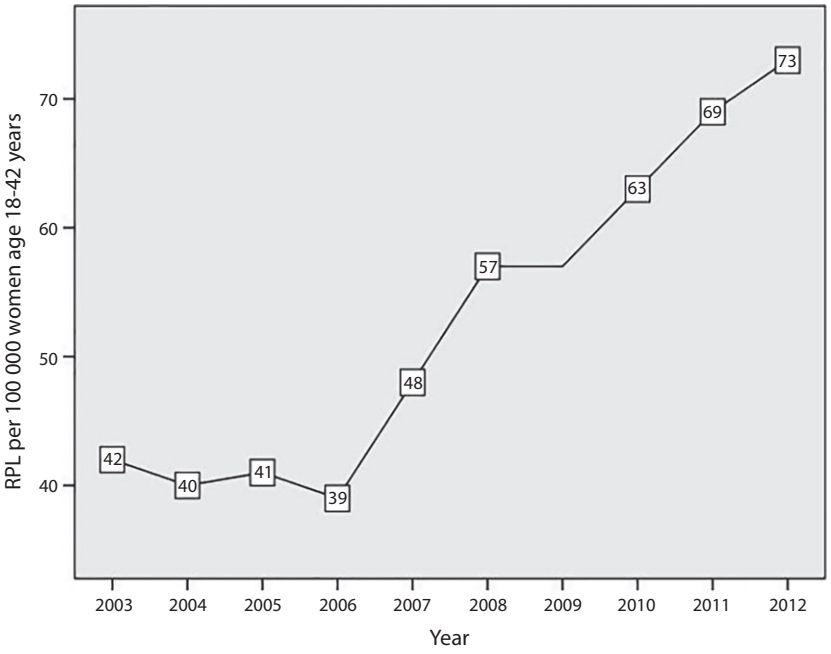

Figure 2. Incidence of recurrent pregnancy loss (RPL) in women aged 18–42 years. The annual incidence from 2003 to 2012 is calculated as the new number of women with RPL per year in the numerator and counts of women each year aged 18–42 years in the denominator.

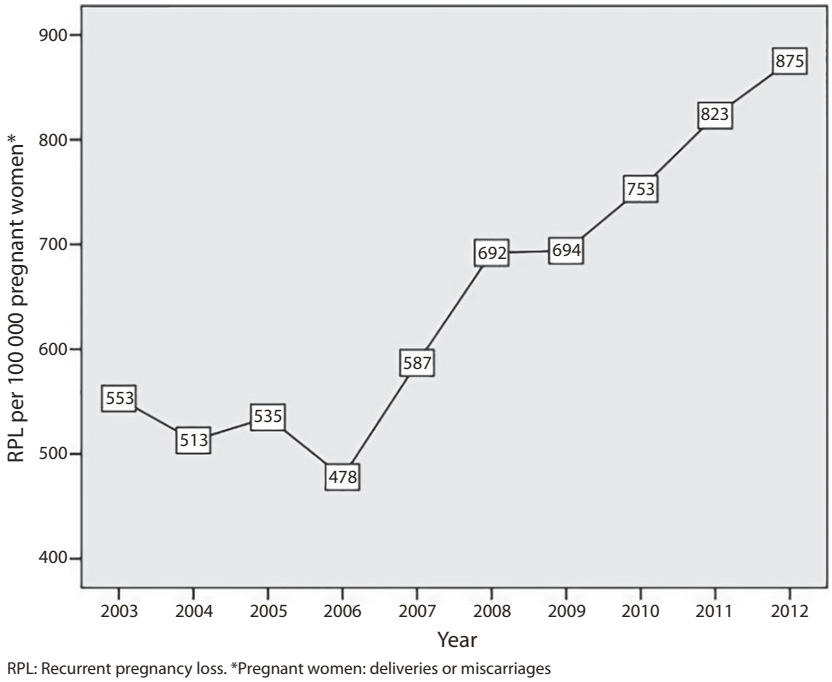

Figure 3. Incidence of recurrent pregnancy loss (RPL) in pregnant women. The annual incidence from 2003 to 2012 is calculated as the new number of women with RPL per year in the numerator and counts of women with pregnancy each year in the denominator.

This manuscript has followed the recommendations of the report "Strengthening the Reporting of Observational Studies in Epidemiology" [24].

The exact incidence of RPL is difficult to estimate as the numbers in both the numerator and the denominator are measures that are subject to uncertainty [19]. In

retrospective studies, selection bias can occur, as these studies are usually based on individuals who have sought help in public or private clinics, and thus may be people with a higher socioeconomic status or more serious medical problems than in the general population [3].

Estimating the incidence of RPL based on register data is likely to underestimate the true incidence, as only miscarriages that are registered in the database are included. We have to accept that a substantial number of undiagnosed early pregnancy losses, including biochemical pregnancies, are not available in the NPR. As women with undiagnosed miscarriages never come into contact with the healthcare system, the clinical relevance of these pregnancy losses is disputed, with some authors [25] supporting the view that these early losses should be ignored in the diagnosis, and other authors stressing their prognostic significance [26].

It would be interesting to compare the incidence of three consecutive miscarriages with two. This was not possible as the diagnosis code of RPL used in the NPR is defined as three consecutive miscarriages.

There is a risk of register misclassifications due to erroneous coding of miscarriage, which may lead to misclassifications regarding the RPL diagnosis. Such errors could include registration of a miscarriage when it is actually a pregnancy of unknown location or when it is not verified by ultrasound, histology or hCG. The authors are currently validating the diagnoses of RPL in the NPR by manual cross-checking of a randomly selected subset of hospital records. However, there is no reason to believe that the frequency of misclassification would be different between the first and second parts of our study period.

Medical authorities providing the register data have a substantial delivery time, which explains why the data ends at 2012. It would be of great interest to complete the study with data from subsequent years.

The significantly increased incidence of RPL over time may in theory be an artifact due to the method of ascertaining data, or may reflect an increasing prevalence of the risk factors for RPL. The inclusion criteria of study group B could be a partial explanation of the lower incidence at the beginning of the study period. None of the women with two miscarriages before 2003, having their third miscarriage in the studied period, was included in study group B, which may in theory explain the lower RPL incidence at the start of the period. However, women with only two miscarriages at the end of the observation period were not included if they experienced the third miscarriage after 2012. A drop in the incidence at the end of the period would then be expected, but this was not seen. Other explanations for the increased RPL incidence could be that the threshold for seeking help by a physician during the process of miscarriage has declined, the availability of ultrasound in early pregnancy has improved, and physicians' attention to the RPL diagnosis has increased. There were no changes in coding instructions for RPL in the study period that can explain the increased incidence.

The annual number of assisted reproductive technology (ART; in vitro fertilization/intracytoplasmic sperm injection) treatments in Sweden has increased from about 10 000 in 2003 to 14 500 in 2010, which may influence the incidence of RPL as this subgroup of women might have a higher frequency of pregnancy loss. About one-third became pregnant after treatment and one-quarter had a live birth [20]. Thus, approximately 19% experienced early pregnancy losses. These figures do not indicate a higher frequency of pregnancy loss after assisted reproductive technology than in the general population. [7]

If the increase in RPL incidence is real, we can only speculate on the reasons. Increasing maternal age when trying to conceive can in theory partly explain our findings, since advanced maternal age is associated with miscarriage due to embryonic aneuploidy. However, the mean age in our population was 33 years over the whole period. If the number in the denominator, for example deliveries plus miscarriages, was decreasing over time, the incidence would increase. However, the number of deliveries instead increased slightly over the study period, with 96 782 births in 2003 and 110 923 births in 2012. Increased prevalence of other risk factors for miscarriage may explain the increasing RPL incidence. Risk factors that could increase substantially during a 10-year period are immunological/inflammatory and environmental factors; further studies are needed to confirm this [27-30]. Other factors that could have changed with time are distribution of ethnicity, mean body mass index and smoking frequency. In 2011, 24% of the childbearing women were from countries outside Sweden, a figure which had increased from 10% in 1973. The data indicate a slight increase of mean body mass index from slightly below 25 to slightly above 25 in 2002 and 2011, respectively, and a decrease of smoking frequency in pregnant women from 10% to 6% in 2002 to 2011. [20] Our study design did not allow us to confirm which, if any, of the above-mentioned factors had changed in our study population. Future studies incorporating appropriate risk factors are needed to explore this question further.

Thirteen percent of women with three or more consecutive miscarriages were wrongly not diagnosed with RPL in the NPR. These women might have missed out on eligible investigation and possible treatment. It is likely that even more women are underdiagnosed than our data allow us to consider. All patients with live births between

the miscarriages were excluded from the cohort, so non-consecutive miscarriages cannot explain why some women were not diagnosed with RPL in the NPR. There are no other characteristics of the NPR regarding the underdiagnosed group that can explain why they did not receive the correct diagnosis as compared with those diagnosed with RPL.

It is difficult to compare our results with other studies as the few estimates made on this subject are based on the prevalence of RPL, not the incidence. It would be misleading to compare the mean incidences of RPL, 0.053% and 0.65%, with prevalence estimates, which are between 0.5% and 2.3% [1–4,23]. Prevalence is more interesting for chronic diseases, such as diabetes. RPL is mainly relevant to women of fertile age; a prevalence rate for all women including those who have passed the fertile age is less important.

When allocating resources for reproductive care and preventive healthcare strategies for women with RPL, knowledge of the incidence is important. The study does not provide information that can support maintaining the definition of RPL as three or more consecutive pregnancy losses, or changing it to, for example two or more losses. We recommend keeping the RPL definition as it is, since we believe this will provide the highest benefit relative to the limited available resources. Changing the definition would also remove the possibility of monitoring changes in RPL incidence in the future.

Conclusion

Our study provides the first estimate of the incidence of RPL based on a whole-nation 10-year cohort. We found a significant increase in the incidence during the period but our study design is limited to speculations on the causes.

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