Prognosis for Live Birth in Women With Recurrent Miscarriage

What Is the Best Measure of Success?

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OBJECTIVE: To establish a method of estimating the proportion of women with a subsequent live birth after a well-defined time period in an open cohort of women referred to a tertiary recurrent miscarriage clinic.

METHODS: We performed a descriptive cohort study with register-based follow-up at a tertiary center for investigation and treatment of recurrent miscarriage in Denmark. All women with primary or secondary recurrent miscarriage referred to the clinic from 1986 to 2008 were included in the study (n=987). Main outcome measures were age-specific and miscarriage-specific proportions of women with a live birth after the first consultation and similar hazard ratios compared with the prognosis in women aged 30–34 years with three miscarriages before the first consultation.

RESULTS: Five years after the first consultation, 66.7% (95% confidence interval [CI] 63.7–69.7) had achieved a live birth, increasing to 71.1% (95% CI 68.0–74.2) 15 years after the first consultation. There was a significantly decreased chance of at least one subsequent live birth with increasing maternal age (log-rank $P<.01$) and increasing number of miscarriages (log-rank $P<.01$) at first consultation.

CONCLUSION: Approximately two thirds of women with recurrent miscarriage referred to a tertiary center succeed in having at least one live birth within 5 years after their first consultation. Our study allows for a descriptive overview of the course of live birth outcome in women with recurrent miscarriage, but not for evaluation of the effect of treatment.

(Obstet Gynecol 2012;119:37–43)
DOI: 10.1097/AOG.0b013e31823c0413

LEVEL OF EVIDENCE: III

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Supported by a clinical research grant from the University Hospital of Aarhus, Aalborg Hospital, Department of Obstetrics and Gynaecology, financing salary for Dr Lund. Part of the salary for Dr Kamper-Jørgensen while working on the study was financed by institutional money from the Fertility Clinic, Copenhagen University Hospital.

Presented at the European Society of Human Reproductive Endocrinology annual meeting, July 3–6, 2011, Stockholm, Sweden, and at the joint meeting between the European Society for Reproductive Immunology and the Early Pregnancy Special Interest Group of the European Society of Human Reproduction and Embryology, August 23–26, 2011, Copenhagen, Denmark.

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Financial Disclosure
Dr. Christiansen has received a fee for one lecture from Leo Pharma Nordic, Malmö, Sweden; and has had travel expenses covered by the European Society of Human Reproduction and Embryology in relation to meetings in the field of early pregnancy. Dr. Lidegaard has received honoraria within the past 3 years for speeches in pharmacoepidemiological issues, including fees from Bayer Pharma Denmark and Novo Nordisk, and is currently an expert witness in a legal case in the United States on oral contraception and venous thromboembolism. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/11

Approximately 1% of women attempting pregnancy are affected by recurrent miscarriage[1] defined as a minimum of three consecutive losses of intrauterine pregnancies.[2] Established and suggested risk factors for recurrent miscarriage are increasing number of successive previous pregnancy losses,[3,4] parental chromosomal anomalies, maternal thrombophilia disorders, and structural uterine anomalies.[2] Finally, increasing maternal age is accepted as the most important risk factor for future miscarriage both in women with recurrent miscarriages[3,4] and in the general population.[5]

An essential part of the management of couples with recurrent miscarriage is to give trustworthy advice on the prognosis for the next pregnancy for the couples to be able to decide for or against further pregnancy attempts. In the field of recurrent miscarriage, however,

a distinct problem is the lack of comparability between estimates of the chance of subsequent successful pregnancy outcomes reported in various studies. The chance of live birth in the next pregnancy in women with three, four, and five previous miscarriages has been reported variably to be between 63 and 87%, 44 and 73%, and 25 and 52%, respectively.[4,6,7] Furthermore, in a group of 325 women with recurrent miscarriages in which 70% achieved a subsequent pregnancy, 75% (n=167 of 222) of the cases resulted in a live birth; however, this study included women with only two previous miscarriages and only reported live birth as an absolute event, not live birth per time unit.[3] Those studies reporting a low miscarriage risk also found a low chance of becoming pregnant and, opposite of those reporting a high miscarriage risk, also found a high chance of becoming pregnant. Thus, the measure of miscarriage risk in the next pregnancy is sensitive to the definition of miscarriage, the degree of monitoring of the women, and to diagnoses of biochemical pregnancies.

To minimize possible biases resulting from intensity of monitoring, we attempted to establish a method for estimating the proportion of women with a subsequent live birth after a well-defined time period in an open cohort of women referred to a tertiary recurrent miscarriage clinic who were monitored for 2 to 24 years.

MATERIALS AND METHODS

Recurrent miscarriage was defined as a minimum of three consecutive pregnancy losses. We divided the patients into two groups: a group in which at least one of the pregnancy losses was verified as intrauterine by ultrasonography or uterine curettage and histology and the remaining by a positive urine human chorionic gonadotropin (hCG) or serum hCG, ultrasonography, or histology and a group with only biochemical pregnancies; all pregnancy losses had been verified only by a positive urine hCG or serum hCG. Pregnancy loss encompassed early miscarriage (less than gestational week 13 6/7) and late miscarriage (gestational week 14 to 21 6/7); birth was classified as delivery of a liveborn neonate after 22 weeks of gestation. Primary recurrent miscarriage encompassed women with only miscarriages before first consultation, whereas secondary recurrent miscarriage included women with at least three miscarriages after one or more live births or stillbirths and no more than two miscarriages before the birth.

The entire cohort comprised women referred with recurrent miscarriage to The Danish Recurrent Miscarriage Clinic from June 1986 to June 2008. Women were included in the study only if they were Danish citizens (enables register-based follow-up) and

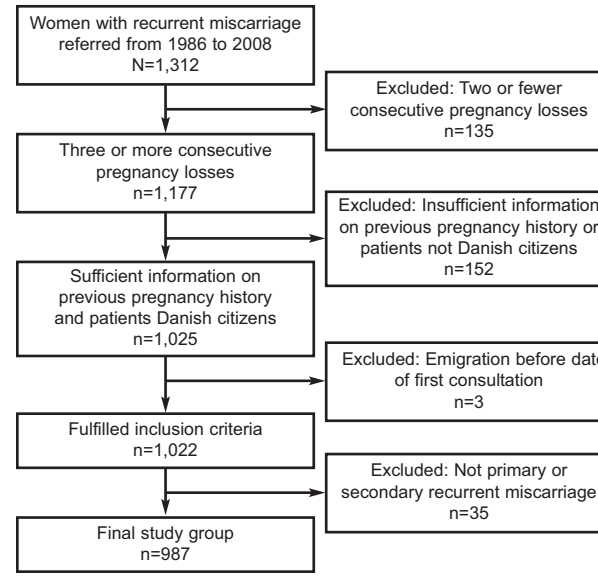

Fig. 1. Selection of study population.
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if the exact study criteria for recurrent miscarriage were met at referral: a minimum of three consecutive pregnancy losses and primary recurrent miscarriage or secondary recurrent miscarriage. Women were monitored by use of National Health Registers to achievement of live birth, migration, death, or end of follow-up (June 30, 2010), whichever came first. Figure 1 illustrates how the final study population of 987 women was selected and baseline characteristics of the cohort are shown in Table 1.

Hospital charts were used to establish reproductive history (miscarriages, stillbirths, and live births) before first consultation at The Danish Recurrent Miscarriage Clinic. If the exact date of first consultation was not available, date of referral was used.

Register information was used to establish exact date of all live births of women in the recurrent miscarriage cohort. All citizens of Denmark are registered in the Danish Civil Registration System (established in 1968) and are assigned a unique personal identification number (the CPR number) enabling linkage of the mother and child. The Civil Registration System provides exact date of death or migration assuring complete follow-up for all women in the recurrent miscarriage cohort. Furthermore, the CPR number permits linkage to other Danish population-based health registers such as the Danish National Birth Registry, which contains records of all births in Denmark. For this study, information on live birth, stillbirth, and gestational age was obtained from the

Table 1. Baseline Characteristics of Women in the Recurrent Miscarriage Cohort According to Age at First Consultation

	Age at First Consultation (y)				
	20–24	25–29	30–34	35–39	40 or Older
Previous live births					
0	40 (6.8)	173 (29.2)	216 (36.4)	139 (23.4)	25 (4.2)
1 or more*	8 (2.0)	73 (18.5)	154 (39.1)	127 (32.2)	32 (8.1)
Previous stillbirths					
0	46 (4.8)	241 (24.9)	363 (37.5)	261 (27.0)	57 (5.9)
1 or more†	2 (10.5)	5 (26.3)	7 (36.8)	5 (26.3)	0 (0)
Previous miscarriages					
3	20 (4.6)	121 (27.7)	159 (36.4)	113 (25.9)	24 (5.5)
4	20 (6.3)	78 (24.4)	122 (38.1)	82 (25.6)	18 (5.6)
5	8 (6.2)	19 (14.6)	50 (38.5)	43 (33.1)	10 (7.7)
6 or more	0 (0)	28 (28.0)	39 (39.0)	28 (28.0)	5 (5.0)
Previous late miscarriages‡					
1 or fewer	46 (5.0)	233 (25.1)	341 (36.8)	252 (27.2)	55 (5.9)
2 or more	1 (2.9)	8 (23.5)	19 (55.9)	6 (17.7)	0 (0)
Biochemical miscarriages only§					
Yes	1 (1.3)	19 (23.8)	36 (45.0)	22 (27.5)	2 (2.5)
No	47 (5.2)	227 (25.1)	333 (36.8)	243 (26.9)	54 (6.0)
Classification					
Primary	38 (6.7)	169 (29.7)	212 (37.3)	127 (22.3)	23 (4.0)
Secondary	10 (2.4)	77 (18.4)	158 (37.8)	139 (33.3)	34 (8.1)
Year at first consultation					
1986–1990	13 (11.9)	41 (37.6)	40 (36.7)	13 (11.9)	2 (1.8)
1991–1995	7 (4.6)	52 (34.2)	59 (38.8)	31 (20.4)	3 (2.0)
1996–2000	11 (7.8)	36 (25.4)	59 (41.6)	30 (21.1)	6 (4.2)
2001–2005	12 (3.4)	83 (23.3)	128 (36.0)	113 (31.7)	21 (5.9)
2006–2009	5 (2.2)	34 (15.0)	84 (37.0)	79 (34.8)	25 (11.0)

Data are n (%).

* Of the 394 women with one or more previous live births, 207 had males only, 154 had females only, and 33 had both males and females.

† Of the 19 women with one or more previous stillbirths, two had males only, three had females only, one had both males and females, and 13 had a stillbirth of unknown sex.

‡ Information on previous late miscarriages was missing for 26 women.

§ Information on biochemical miscarriages was missing for three women.

establishment of the registry (January 1, 1973) until the end of follow-up (June 30, 2010).

When referred to the clinic, the first consultation was used to obtain a thorough medical history including as much information on pregnancy history as possible. In the entire study period, most patients had, at their local hospital before referral, been investigated for uterine malformations by hysterosalpingography, hysteroscopy, or uterine hydrosonography with no significant anatomic abnormalities being detected. Patients with no investigation of the uterine cavity at the time of referral had uterine hydrosonography done at our clinic. Parental karyotyping was performed in almost all (more than 95%) of the couples; however, referral to preimplantation genetic diagnosis was only performed in five of the cases with abnormal parental karyotype and only two children were born after this procedure. Before 2000, the work-up, in addition to uterine and chromosome investigations, only consisted of screening for lupus anticoagulant, anticardiolipin antibodies, and antinuclear antibodies. From 2000 onward, the routine laboratory work-up was extended to include screening for thyroid disease, mannose-binding lectin deficiency, hereditary thrombophilias, and, in case of cycle irregularities, endocrine screening: androgens, luteinizing hormone, follicle-stimulating hormone, and prolactin.

Throughout the study period, all women seen at the clinic were encouraged to attempt pregnancy and received supportive care by means of frequent hCG measurements and frequent ultrasonographic scans (approximately every second week) until week 16 after which the pregnancy was surveilled by the obstetric ward where the birth was planned to take place. If there was an additional infertility problem, the women were referred to treatment with assisted reproductive therapy (in vitro fertilization, intracytoplasmic sperm injection, or intrauterine insemination with the partner's sperm).

Until 2000, among all patients referred to the clinic approximately, 20% were treated with partner or third-party lymphocytes, approximately 20% with intravenous immunoglobulin, primarily as part of placebo-controlled trials,[8,9] and an estimated less than 3% were treated with heparin, mainly as a result of the presence of the lupus anticoagulant. After 2000, treatment with intravenous immunoglobulin was mainly suggested to women with recurrent miscarriage and more than four miscarriages or to women with repeated intrauterine fetal death. Since 2005, an increasing number of patients were treated in our clinic with vaginal progesterone until gestational week 10 (if plasma progesterone levels in weeks 5–6 were low or rapidly decreasing) or prednisone until gestational week 7 (particularly women with recurrent miscarriage conceiving after assisted reproductive technology), whereas we have never advised women to take aspirin. Furthermore, a few women with late miscarriages, in whom cervical insufficiency was thought to be a cause of the miscarriages, were treated with cerclage.

In the period from 2004 to 2006, we uniformly counted information from the clinic's annual reports on the treatment given to all women who became pregnant while attending the clinic (before 2004 and after 2006 annual counts have not been assessed as uniformly as in 2004–2006). Two hundred thirty-three pregnancies were monitored (a few women may have received treatment in more than one pregnancy), of which 34.3% included treatment with intravenous immunoglobulin alone, 35.2% with intravenous immunoglobulin in part combined with prednisone or third-party lymphocytes, 3.4% with third-party lymphocytes alone, 4.3% with heparin mainly combined with intravenous immunoglobulin, 5.2% with other treatment (indomethacin in gestational weeks 16–28 or folic acid), and 17.6% with only supportive care or vaginal progesterone. If the first pregnancy resulted in a miscarriage, many women cut contact with the clinic and thus information about possible treatment in subsequent pregnancies is incomplete; some may have received prednisone, progesterone, heparin, or aspirin in other clinics, whereas intravenous immunoglobulin was only given in our clinic.

Women were monitored from time of first visit to the recurrent miscarriage clinic to the time of live birth, migration, or death, whichever came first. The chance of a live birth among women diagnosed with recurrent miscarriage was evaluated in two sets of analyses. First, we estimated the proportion of women who had given birth to a liveborn child according to time elapsed since first consultation at the recurrent miscarriage clinic using a Kaplan-Meier estimator. The proportion of women who gave birth and belonging 95% confidence intervals (CIs) was estimated using the LIFETEST procedure. Differences between subgroups were tested with log-rank tests. Next, to quantify the relative difference in chance of a live birth after first consultation at the recurrent miscarriage clinic among subgroups of women, we estimated hazard ratios and belonging 95% CIs in Cox proportional hazards regression models. Because the scope of the study was descriptive rather than analytical, we chose not to adjust for potential confounders. Modeling was done using the PHREG statement, with time in the study as the underlying time scale. The main effect of relevant variables was estimated as well as the interaction between age at the first consultation at the clinic and the number of previous miscarriages. Interaction was evaluated using a likelihood ratio test comparing the fit of the model including the main effect of age at first consultation at the clinic only with a model also including the interaction term between age at first consultation at the clinic and the number of previous miscarriages.[10] In cases in which the date of first consultation was preceded by a date of migration, the participant was excluded from the analyses. All data management and analysis was done in SAS 9.2.

Permission to perform the register withdrawal was given by the Danish Data Protection Agency (reference number 2008-41-2666). Because this study was based on register data and hospital charts, approval by an institutional review board was not needed according to Danish legislation.

RESULTS

The 987 women in the study group gave birth to 665 children after the first consultation and lived a total of 3,881.6 person-years; the average number of person-years at risk was 3.93. The median age at first consultation was 32.7 (interquartile range 29.4–36.1, range 20.0–45.9) years, and the median number of pregnancy losses before first consultation was four (interquartile range 3–4; range 3–6).

As depicted in the Kaplan-Meier plot in Figure 2, 66.7% (95% CI 63.6–69.7) of the 987 women in the cohort had achieved a live birth 5 years after first consultation increasing to 71.1% (95% CI 68.0–74.2) 15 years after the first consultation. In the group of women referred until the end of 1999 (n=378 of 987), 66.2% (95% CI 61.4–70.9) had achieved a live birth 5 years after first consultation with a corresponding proportion of 66.6% (95% CI 62.6–70.5) in the group of women referred from the beginning of 2000 (P=.43).

Figure 3 illustrates the chance of a live birth according to years elapsed after first consultation for different ages at time of first consultation. There was a significant

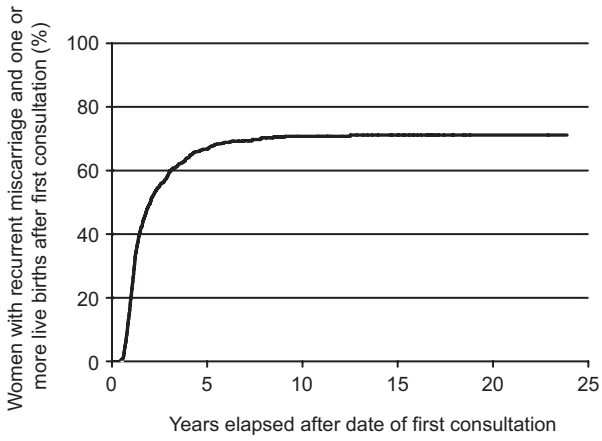

Fig. 2. Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation.

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overall difference in outcome of at least one live birth between the different age groups (log-rank $P<.01$). Thus, in women aged 40 years or older, 41.7% (95% CI 29.8–56.1) had achieved a live birth 5 years after first consultation as opposed to 81.3% (95% CI 69.2–90.7) of the women aged 20–24 years at the time of first consultation. For instance, compared with the reference group of women aged 30–34 years at the time of first consultation (hazard ratio of 1), the hazard ratio for giving birth to at least one child 5 years after first consultation was 1.43 (95% CI 1.03–1.98) in women aged 20–24 years decreasing to 0.55 (95% CI 0.36–0.83) in women aged 40 years or older (data not shown).

There was also a significant overall difference in chance of a live birth by increasing number of miscarriages before first consultation (log-rank $P<.01$). As seen in Figure 4, 71.9% (95% CI 67.5–76.1) of the women with three miscarriages before first consultation had achieved a live birth 5 years after first consultation as opposed to 50.2% (95% CI 40.5–60.8) of the women with six or more previous miscarriages. Correspondingly, the hazard ratio for giving birth to at least one child 5 years after the first consultation was 0.55 (95% CI 0.41–0.74) among the women with six or more previous miscarriages compared with the reference group of women with three previous miscarriages (hazard ratio of 1; data not shown).

We found no evidence of interaction between the number of previous miscarriages and age at first consultation (likelihood ratio $P=0.12$). The hazard ratios of having achieved a live birth 5 years after referral according to number of miscarriages before the first consultation and age at first consultation can be seen in Table 2. In the chosen reference group of women with three previous miscarriages aged 30–34 years at the time of first consultation, the hazard ratio of 1 for achieving at least one live birth 5 years after first consultation corresponded to an absolute proportion of 69.9% (95% CI 62.5–77.1) of the women (data

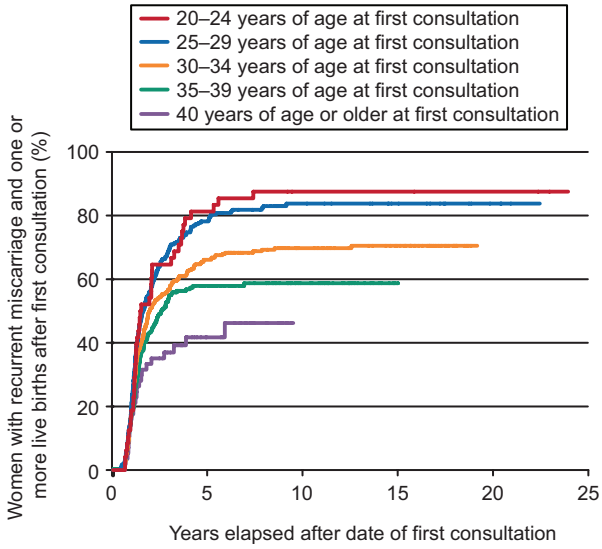

Fig. 3. Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by age at first consultation.

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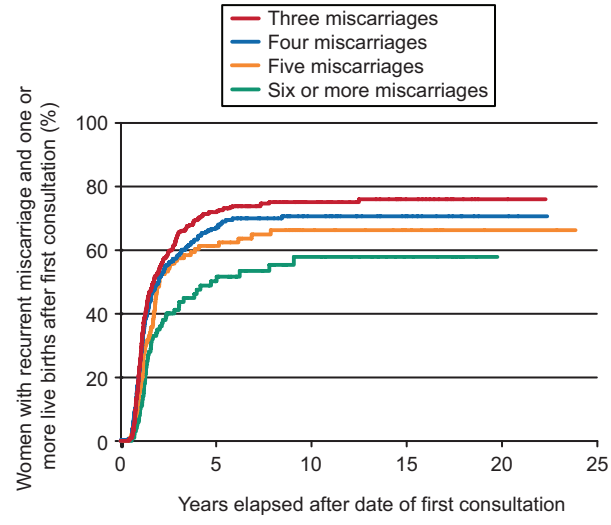

Fig. 4. Kaplan-Meier plot showing percentage of women in the recurrent miscarriage cohort who have had at least one live birth after first consultation by number of miscarriages before first consultation.

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Table 2. Hazard Ratio (95% Confidence Interval) of Achieving a Live Birth After Referral According to Age at First Consultation and Number of Previous Miscarriages

No. of Previous Miscarriages	Age at First Consultation (y)				
	20–24	25–29	30–34	35–39	40 or Older
3	1.28 (0.78–2.11)	1.50 (1.15–1.96)	1 (reference group)	0.81 (0.60–1.10)	0.48 (0.26–0.89)
4	1.93 (1.20–3.11)	0.99 (0.72–1.36)	0.95 (0.72–1.26)	0.67 (0.47–0.95)	0.88 (0.46–1.68)
5	0.48 (0.18–1.29)	1.51 (0.92–2.48)	0.79 (0.53–1.18)	0.76 (0.50–1.17)	0.32 (0.10–1.00)
6 or more	NE	0.80 (0.49–1.30)	0.55 (0.34–0.88)	0.51 (0.29–0.91)	NE

NE, not estimable.

not shown). The corresponding absolute proportions of women with a subsequent live birth was 50.6% (95% CI 35.7–67.5) in women aged 30–34 years and at least six previous miscarriages at the time of first consultation, 42.0% (95% CI 25.2–64.0) in the group of women aged 40 years or older with three previous miscarriages and 85.0% (95% CI 66.5–96.3) in the group of women with three previous miscarriages aged 20–24 years.

Looking at other clinical and demographic factors at time of first consultation, the hazard ratio for a live birth 5 years after the first consultation in women with two or more late miscarriages (in addition to at least one early miscarriage) compared with the remaining study group (hazard ratio of 1) was 0.87 (95% CI 0.58–1.32). Furthermore, in women with secondary recurrent miscarriage and a previous birth of a boy, the hazard ratio for a live birth 5 years after first consultation was 0.80 (95% CI 0.62–1.03) compared with the reference group of women with secondary recurrent miscarriage and a previous birth of a girl (hazard ratio of 1). Finally, looking at the subgroup of women with recurrent miscarriage and a history of biochemical pregnancies only compared with the rest of the study group (hazard ratio of 1), the hazard ratio for a live birth was 0.78 (95% CI 0.58–1.04).

DISCUSSION

This is a cohort study with long-term follow-up investigating the chance of a live birth per time unit subsequent to first consultation among women with recurrent miscarriage referred to a tertiary recurrent miscarriage clinic. Approximately two thirds of the study cohort achieved a live birth after a first consultation at the clinic and the majority of the deliveries took place within the first 5 years after a first consultation.

In a previous study by Brigham et al,[3] the overall predicted percentage success rate (defined as survival beyond 24 weeks of gestation) in a group of women pregnant after referral to a recurrent miscarriage clinic was 75% (follow-up for up to 10 years). The corresponding proportion with at least one live birth 5 years after first consultation was in our study 66.7% (95% CI 63.7–69.8). Furthermore, in the subgroup of women with three previous miscarriages aged 30–34 years, the predicted percentage success rate of a subsequent pregnancy was 80% (95% CI 74–86) in the study by Brigham et al, whereas 69.8% (95% CI 32.4–76.9) of the women in our study had at least one liveborn child 5 years after the first consultation. Thus, overall we can report lower live birth rates compared with the previous study be Brigham et al, which is most likely explained by different definitions of recurrent miscarriage. Recurrent miscarriage was defined as a minimum of three consecutive miscarriages in our study, whereas 24% of the study group in the study by Brigham et al were patients with only two miscarriages. Other differences between the two studies were differences in the exclusion criteria in which patients with some established risk factors for recurrent miscarriage (for example, parental chromosomal translocations) and patients with second-trimester losses were included in our study, whereas they were excluded from the study by Brigham et al.

A major strength of the present study was the follow-up on the primary outcome of live birth for all women by use of the National Danish Birth Registry. Furthermore, by linkage to the Danish Civil Registration System, we were able to censor women who migrated, died, or turned 50 years old at the relevant date. This gave us the opportunity of monitoring women for as long as 24 years. In our opinion, we present a more transparent and well-defined outcome measure of a chance of a live birth as opposed to miscarriage risk in the next pregnancy. We believe that the outcome of live birth per time unit is more relevant for the patients and less prone to bias according to the intensity of monitoring.[11] The main limitations of our study regard 1) lack of adjustment for relevant risk factors for recurrent miscarriage; and 2) lack of adjustment for the effect of treatment. Regarding the first point, in the earlier part of the study period, some risk factors were not known and therefore not investigated as part of the routine work-up of

the patients (for example, the hereditary thrombophilia disorders) and also the cutoff values for positivity for anticardiolipin antibodies have changed several times during the study period.[12] Thus, we are not in this study able to discriminate between unexplained and explained recurrent miscarriage, a question better addressed in a study with a shorter follow-up period allowing for uniform diagnostic criteria and analysis of risk factors. The lack of information on treatment is a further limit of the study; however, the study was not designed to address the effect of treatment and including information on this in the study would introduce severe bias because treatment was not given systematically or entirely as part of randomized controlled trials. Furthermore, we do not have information on treatment given in all subsequent pregnancies, if any, because some of the women who miscarried in the first pregnancy after referral did not contact the clinic afterward. Thus, this study was given the descriptive scope of the study neither designed for individual risk estimation nor to evaluate whether there had been an effect of specific treatments. The effect of treatment should be addressed by means of randomized controlled trials. Furthermore, this study does not answer as to why approximately one third of the women in the recurrent miscarriage cohort ended up without a live birth. One reason could be continuation of the miscarriages in all subsequent pregnancies, but other reasons could be inability to conceive as a result of increased age or tubal damage caused by postabortion pelvic inflammation, the couple may have given up on further pregnancy attempts resulting from anxiety of another miscarriage, and finally the couple may have divorced. A 5-year follow-up study with prospective recording of all pregnancy outcomes would be the ideal setting to accommodate this limitation.

Our study looks at long-term live birth outcome instead of outcome per pregnancy in women with recurrent miscarriage and we have suggested a method for addressing this question. The results of the study can be used to give a descriptive overview of the course of live birth outcome in women with recurrent miscarriage and the effect of demographic risk factors present at the time of first consultation.

To conclude, approximately two thirds of women with recurrent miscarriage had at least one live birth after first consultation at the recurrent miscarriage clinic with the majority of the children being born within 5 years of the first consultation. The proportion of women with a subsequent live birth was negatively affected by increasing number of previous miscarriages and increasing age at first consultation. The study is descriptive with the aim of establishing the overall long-term prognosis in women with recurrent miscarriage; however, it does not assess the effect of treatment and is not directly applicable for counseling at the individual patient level. To improve the possibilities of earlier identification of those women with recurrent miscarriage at risk of never achieving a live birth and to further identify and confirm those factors that play an important role in the pathogenesis of recurrent miscarriage, we suggest conducting a prospective 5-year follow-up-study with the same methodological approach as this study, however looking also at the effect of established and suggested demographic and laboratory risk factors for recurrent miscarriage.

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