Live Birth Rate According to Maternal Age and Previous Number of Recurrent Miscarriages

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Keywords
Live birth rate, maternal age, previous number of miscarriage, recurrent miscarriage

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This study was supported by the Ministry of Health, Labour and Welfare.

Submitted July 7, 2009;
accepted August 11, 2009.

Citation
Sugiura-Ogasawara M, Ozaki Y, Kitaori T, Suzumori N, Obayashi S, Suzuki S. Live birth rate according to maternal age and previous number of recurrent miscarriages. Am J Reprod Immunol 2009; 62: 314–319

doi:10.1111/j.1600-0897.2009.00741.x

Problem
In Japan, marital age and women's age at the first pregnancy are continuing to increase year by year. However, information concerning subsequent live birth rate according to maternal age and number of previous recurrent miscarriages is limited.

Method of study
We studied a total of 1250 unexplained patients suffering two or more consecutive miscarriages. We examined the live birth rate at the first pregnancy and the cumulative success rate for birth of at least one child after examination.

Results
The live birth rate of women in their 40s was 58.1%, which was similar to that of women who were 35–39 years old (58.4%) at the first pregnancy, as found after examination. From logistic regression, women's age and the number of previous miscarriages independently decreased the live birth rate in subsequent pregnancies (p_s) as well as cumulative pregnancies (p_c), as follows:

$$\text{logit}(p_s) = 3.964 - 0.0652 \times (\text{age}) - 0.408 \times (\text{previous number of miscarriages})$$

$$\text{logit}(p_c) = 6.806 - 0.1130 \times (\text{age}) - 0.514 \times (\text{previous number of miscarriages}).$$

Conclusion
The information concerning the live birth rate can be given to each patient before subsequent pregnancy.

Introduction

Marital age and women's age at the first pregnancy are continuing to increase year by year in Japan. Also, total fertility rate has decreased and is now 1.34 in Japan, compared to 2.10 in the USA in 2007.[1] This problem is called as 'Shosika' in Japanese, which means childless society, and is common to many countries. Increasing maternal age is also associated with increase risk of infertility, miscarriage, and poor prognosis in pregnancy, such as pre-eclampsia.[2]

Established causes of recurrent miscarriages are abnormal chromosomes in either partner, particularly translocations, as well as antiphospholipid antibodies (aPLs) and uterine anomalies.[3–5] An abnormal embryonic karyotype is also causative of recurrent miscarriage and has been reported in about 25–50% of aborted conceptions.[6–8] The relatively wide range reported may reflect differences in maternal mean age and previous mean number of miscarriages, as these could conceivably exert an influence.

Recently, many patients aged more than 40 years old are presenting at hospital requesting for examinations for recurrent miscarriages. In an earlier study, the percentage of clinical pregnancies that failed to result in a live birth was found to rise from 14% for patients under 35 years of age, to 19% at age 35–37 years, 25% at age 38–40 years, and 40% after age 40 years, in sporadic abortion.[9]

However, information concerning prognosis in recurrent miscarriage women is limited. Therefore, this study was conducted to assess subsequent live birth rate on a prospective basis, according to maternal age and previous number of miscarriages.

Material and methods

We studied 1250 patients with a history of two or more[2–12] consecutive miscarriages after excluding 182 patients with congenital uterine anomalies, chromosome abnormalities, and persistent aPLs.

Hysterosalpingography (HSG); chromosome analysis for both partners; determination of aPL; including lupus anticoagulant and β2 glycoprotein I-dependent anticardiolipin antibodies;[10] and blood tests for hyperthyroidism, diabetes mellitus, and hyperprolactinemia were performed for all cases before subsequent pregnancy. The subjects were all examined between January 1990 and December 2007 at Nagoya City University Hospital. Of the total 1432 patients, 48 had congenital uterine anomalies, excluding arcuate uteri, while 81 had structural chromosome abnormalities, including 69 translocations in either partner. A total of 56 patients exhibited persistent aPLs and were treated with low-dose aspirin and heparin combined therapy. A single patient had both congenital uterine anomaly and translocation. Two had both structural chromosome abnormalities and aPLs.

All patients became pregnant at least one more time and their pregnancies were followed up. Those with a history of only two miscarriages received tender loving care with no medication. Patients with three or more unexplained miscarriages received paternal mononuclear cell immunization from 1990 to 1999, a biologic response modifier from 1992 to 2004,[11] and low-dose aspirin or no medication from 2000 to 2007, respectively.

Gestational age was calculated from basal body temperature charts. Ultrasonography was performed once or twice a week from gestational weeks 4 to 8. Dilation and curettage were performed when miscarriages were diagnosed, and the karyotypes of aborted conceptuses were determined using a standard G-banding technique, to allow the comparison of abnormal karyotype rates between groups with different ages. The study was approved by the Research Ethics Committee at Nagoya City University Medical School.

To examine the individual effect of age and previous number of miscarriages on live birth for the first subsequent and cumulative pregnancies, we performed logistic regression using the SAS system (SAS Institute Inc., Cary, NC, USA). The effect of each treatment on live birth for the first subsequent pregnancies was also examined. $P < 0.05$ was considered to be statistically significant.

Results

Thus, a total of 1250 patients with an unexplained etiology were studied. The mean (S.D.) ages of women suffering from recurrent miscarriages are shown in chronological order in Table I, and are found to be significantly increasing with time ($P = 0.002$). However, the mean number of previous miscarriages did not vary with time.

Subsequent pregnancy outcomes are summarized in Table II. Live birth rate of the first pregnancy after examination significantly decreased as the maternal age increased. The live birth rate of women in their 40s was 58.1%, which was similar to that of women who were 35–39 years old (58.4%) at their first pregnancy, as found after examination. Cumulative success rate also decreased with women's age at the first pregnancy. However, 65.1% of patients in their 40s could cumulatively give birth to a live baby within the follow-up period.

Table I Mean Age of Women Suffering Recurrent Miscarriages in Chronological Order

	1990–94	95–99	2000–04	05–07
Mean (S.D) age*	29.9 (38)	30.5 (4.0)	31.3 (4.4)	33.4 (4.2)**
No. of previous miscarriages	2.6 (0.9)	2.7 (1.0)	2.6 (0.9)	2.6 (1.6)

*Age at the first pregnancy after the examination.
**The mean (S.D.) ages of women significantly increased with time ($P = 0.002$).

Rates for an abnormal chromosome karyotype in aborted concepti in women aged ≥ 35 and ≤ 34 years were 75.8% (50/66) and 51.0% (75/147), respectively, the difference being highly significant ($P = 0.00119$).

Live birth rates for individuals in their 40s are summarized in Table III. Values with the previous number of miscarriages are given in Table IV. Both live birth rate at the first pregnancy and cumulative live birth decreased significantly as the number of previous miscarriages increased.

From logistic regression, age at and number of previous miscarriages independently decreased the live birth rate of subsequent pregnancy ($P < 0.000$, 95% confidence interval 1.034–1.098; $P < 0.000$, CI 1.324–1.712) and that of cumulative pregnancy ($P < 0.000$, CI 1.065–1.152; $P < 0.000$, CI 1.439–1.914). Number of previous live birth independently increased the live birth rate of cumulative pregnancy ($P = 0.003$, CI 1.198–2.476), but not subsequent pregnancy.

No effect of low-dose aspirin, paternal mononuclear cell immunization, and biologic response modifier on the live birth for the first subsequent pregnancies could be found from logistic procedure.

The live birth rate of subsequent pregnancy (p_s) and cumulative pregnancy (p_c) could be calculated as follows:

$$\text{logit}(p_s) = 3.964 - 0.0652 \times (\text{age}) - 0.408 \times (\text{previous number of miscarriages})$$

$$\text{logit}(p_c) = 6.806 - 0.1130 \times (\text{age}) - 0.514 \times (\text{previous number of miscarriages}).$$

As logit is the natural logarithm of odds, and odds is the ratio of probability over (1-probability), p_s is calculated as $\exp(\text{logit}(p_s))/[1 + \exp(\text{logit}(p_s))]$. The areas under receiver-operating characteristics curves, meaning the cumulative diagnostic accuracy of the regression of p_s and p_c, were 0.642 and 0.713 respectively.

From logistic regression, age independently ($P = 0.001$, CI 0.821–0.949) increased and number of previous miscarriages independently ($P = 0.001$, CI 1.179–1.879) decreased the abnormal embryonic karyotype rate.

Discussion

From our study, the age of women suffering from recurrent miscarriage in the Japanese population is increasing year by year, in line with increase of marital age and age at the first pregnancy.[1] Maternal age is well-known to be a significant risk factor for spontaneous abortion and Anderson et al. reported that the risk according to maternal age at conception follows a J-shape curve, with a steep increase after 35 years of age, from their analysis of a database of 634,272 women and 122,1546 pregnancies in Denmark.[12] They concluded that spontaneous abortion is high in women in their late 30s or older, irrespec-

Table II Subsequent Live Birth Rate According to Women's Age

Women's age	18–24	25–29	30–34	35–39	40–45
Mean number of previous miscarriage	2.4 (0.6)	2.5 (0.8)	2.8 (1.2)	3.1 (1.4)	2.9 (1.6)
Live birth rate at the first pregnancy after examination	78.1% (32/41)	76.9% (357/464)	66.7% (337/505)	58.4% (115/197)	58.1% (25/43)
Cumulative success rate	92.7% (38/41)	92.2% (428/464)	83.8% (423/505)	75.1% (148/197)	65.1% (28/43)
Abnormal embryonic karyotype	50% (2/4)	47.9% (23/48)	52.6% (50/95)	80.0% (44/55)	54.5% (6/11)

Table III Live Birth Rates in Women Aged 40 years and Over

Women's age	40	41	42	43	44	45
Live birth rate at the first pregnancy after examination	66.7% (12/18)	87.5% (7/8)	50.0% (4/8)	33.3% (1/3)	33.3% (1/3)	0% (0/2)
Cumulative success rate	72.2% (13/18)	87.5% (7/8)	62.5% (5/8)	33.3% (1/3)	33.3% (1/3)	50.0% (1/2)

Table IV Subsequent Live Birth Rate According to the Previous Number of Miscarriages

Previous No. of miscarriages	2	3	4	5	6	7
Mean (S.D.) maternal age	30.3 (4.1)	31.2 (4.1)	32.2 (4.1)	33.5 (3.7)	33.8 (4.8)	33.8 (3.9)
Live birth rate at the first pregnancy after examination	76.3% (486/638)	66.1% (298/451)	59.0% (59/100)	53.3% (16/30)	31.3% (5/16)	13.3% (2/15)
Cumulative success rate	91.2% (582/638)	82.9% (374/451)	76.0% (76/100)	73.3% (22/30)	56.3% (9/16)	20.0% (3/15)
Abnormal embryonic karyotype	68.3% (56/82)	56.5% (48/85)	65.0% (13/20)	25.0% (l/4)	28.65% (2/7)	20.0% (2/10)

tive of the number of previous miscarriages, parity, or calendar period.

The incidence of recurrent miscarriage, defined as three or more spontaneous abortions, is about 1% in couples.[13] The observed incidence is much higher than that expected by chance alone (0.34%).[14] Translocation in either partner is one of the most important causes of recurrent miscarriage and the prognosis of subsequent pregnancy (32–63%) in couples with abnormal embryonic karyotype is poorer than that in couples with normal chromosome karyotypes.[2,15] Live birth rate of pre-implantation genetic diagnosis was reported to be 23.7% (per oocyte retrieval).[16] However, the cumulative prognosis of translocation carriers is equal to that in couples with normal chromosome karyotypes (83%).[17] Congenital malformations such as septate, bicornuate or unicornuate uteri, and didelphys were found in 3.2% of our patients. The incidences of clear congenital uterine anomalies in patients with a history of recurrent miscarriages have been reported to be 1.8–20.1%, with the arcuate uterus excluded, and thus higher than the 2.2% documented for fertile women (28 of 1289,[18]). Our recent study proved that congenital uterine malformations cause miscarriage associated with a normal embryonic karyotype in recurrent miscarriage cases.[5] Antiphospholipid syndrome (APS) is the most important treatable cause of recurrent miscarriage,[4] with aspirin plus heparin as the most effective therapy.[19] Thus, we excluded cases with abnormal chromosome karyotype in either partner, congenital uterine malformation, and APS from the analysis in this study.

Historically, recurrent miscarriage has also been attributed to genetic, structural, infective, endocrine, immune, or unexplained causes.[20] Infective causes remain speculative. Well-controlled diabetes does not appear to be a risk factor[21] and several women diagnosed as suffering from this disease were treated with insulin before conception. Patients with hyperthyroidism or hypothyroidism were controlled, although no association between the presence of thyroid autoantibodies and recurrent miscarriages has been found.[22] Patients with three or more unexplained miscarriages were treated with paternal mononuclear cell immunization or low-dose aspirin in this study. However, these treatment methods were earlier found to have no benefit in preventing miscarriages.[23,24] In this study, we could find no effect of paternal mononuclear cell immunization, biological response modifier, and low-dose aspirin on the live birth for the first subsequent pregnancies using logistic procedure. Thus, we did not enter the effect of various treatments on the live birth.

Embryonic aneuploidy is the most important cause of miscarriage before 10 weeks' gestation and our previous study showed that 70% of sporadic spontaneous abortions were caused by an abnormal embryonic karyotype.[6] A recent microarray comparative genomic hybridization indicated that about 80% of sporadic spontaneous abortions were caused by an abnormal embryonic karyotype.[25] Thus, the incidence of patients with repeated miscarriages caused by abnormal embryonic karyotype can be calculated to be $(0.8)^n$ in n consecutive miscarriages. About 51% of patients with a history of three miscarriages can be expected to experience three miscarriages caused by abnormal embryonic karyotype. In fact, about 50% of the karyotypes were abnormal in aborted concepti of the recurrent miscarriage group.[6] The incidence of abnormal embryonic or fetal karyotype might be much higher than those of APS or translocations, although this cannot be specified because aborted concepti are seldom karyotyped clinically.

Abnormal embryonic karyotype is well-known to be a predictor of subsequent success.[6–8] Abnormal rates in recurrent miscarriages were found to be 25–52%.[6–8,26,27] The variable results depend on

maternal age and number of previous miscarriage. Both maternal age and reproductive history are independent predictors of further pregnancy outcome.[26] This is in line with the findings of this study in recurrent miscarriage. If we can provide strong evidence of definite success, this would have a major cheering effect on patients. Several couples in our experience gave up trying to conceive after recurrent miscarriages because they were under the misunderstanding that it would be impossible for them to have a live baby. Psychological tender loving care might be the most important requirement to continue conceiving till live birth results.[28]

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