Conception delay and spontaneous and indicated preterm birth among primiparous women in Japan

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Aim: To examine whether a longer time to pregnancy is associated with preterm births distinguished as either spontaneous or indicated delivery.

Methods: A cross-sectional survey was conducted targeting parous women aged 20-44 years old residing across Japan whose first-born children were singletons. Information on reproductive history including time to pregnancy (TTP) and use of assisted reproductive technology (ART) was collected using internet-based questionnaire. A delivery was judged spontaneous if the mother had either labor and/or membrane rupture at hospital admission. Multinomial logistic regression analyses were performed to estimate odds ratios and 95% confidence intervals (CI) for spontaneous and indicated preterm birth at < 34 or at < 37 weeks of gestation while adjusting for potential confounders.

Results: The analytic sample was n=4,208 mothers with first-born singletons. After adjusting for age, use of ART, and other possible confounders, women with TTP of 12+ months had significantly higher odds of spontaneous preterm birth at < 34 weeks (OR 4.55, 95% CI 1.10-18.77) but not at < 37 weeks (OR 1.07, 95% CI 0.65-1.75), compared to those with TTP of < 6 months. Women with unknown TTP tended to have higher odds of spontaneous preterm birth at < 34 weeks (OR 3.67, 95% CI 1.02-13.19) and at < 37 weeks (OR 1.38, 95% CI 0.98-1.96), though not statistically significant. There was no significant association with TTP and indicated preterm birth.

Conclusions: Compared to mothers with shorter TTP, those with longer TTP are more likely to experience spontaneous preterm birth.

Key words: infertility, spontaneous preterm birth, indicated preterm birth, time to pregnancy, BMI

I Introduction

The rates of preterm birth, defined as delivery fewer than 37 completed weeks of gestation, have been increasing in a number of countries ¹,². In 2010, the estimated rate of preterm birth was 11.1% for the whole world³, emphasizing the importance to understand the underlying factors affecting the increasing rate.

Several studies have recently suggested that pregnancies following assisted reproductive technology (ART), i.e. ovulatory drugs, artificial insemination, in vitro fertilization and micro–insemination, are associated with higher risks of preterm

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birth compared with natural pregnancies\(^3\)–\(^8\). On the other hand, some studies have indicated that infertility itself can be an underlying factor for the increased risk of preterm birth even without the use of ART\(^9\)–\(^14\). A meta-analysis study that examined the association between time to pregnancy (TTP), defined as the duration (in months) between the discontinuation of contraception and conception\(^5\), and the risk of preterm birth showed that women with a TTP of > 12 months had higher risk of preterm birth at < 37 weeks of gestation compared with women with a TTP of 12 months or shorter (OR: 1.31, CI: 1.21–1.42)\(^16\).

It has been hypothesized that some physiological characteristics common in women with longer TTP are associated with increased risks of spontaneous preterm parturition and/or clinical conditions that require induced preterm birth\(^5\)\(^9\)\(^10\)\(^14\)\(^16\)\(^17\), but the exact mechanisms linking conception delay to preterm birth are unknown. To the best of our knowledge, it remains unknown to date whether a longer TTP is associated with spontaneous, indicated, or both types of preterm birth, because previous studies that investigated this association did not distinguish between the two types\(^5\)\(^9\)\(^10\)\(^13\)\(^16\)\(^18\).

Understanding of how specific type of preterm birth, i.e. spontaneous or indicated, is associated with delayed conception can give further insights into the possible mechanisms, which will eventually help to understand causes of preterm births. This information can be extracted using self-administered questionnaire, for example, by modifying Harlow et al.’s\(^19\) definition to differentiate between spontaneous and indicated preterm birth. Specifically, spontaneous preterm birth was defined as preterm delivery in which the membrane rupture and/or labor was present at the time of admission for delivery, while indicated preterm birth was defined as preterm delivery in which there was no spontaneous rupture of membranes or preterm labor at the time of admission, regardless of the route of delivery.

To address this research gap, the objective of the current study is to examine the association between the time to pregnancy and preterm births classified as either spontaneous or indicated.

### II Material and methods

A cross-sectional study was conducted based on a self-administered Internet-based survey targeting the registered monitors of Rakuten Research, Inc., an established market research firm in Japan. The Internet-based questionnaire survey enabled the collection of detailed information on birth outcomes and risk factors targeting participants residing across Japan with various socio-economic positions. The monitors of Rakuten Research consist of individuals who use any services provided by Rakuten business group (such as online shopping and travel reservation) and who have voluntary registered to become research monitors. As of January 2016 there were 2,267,602 monitors across Japan\(^20\). These monitors receive invitations to various surveys by email. They choose which survey to participate and upon completing they receive points as a reward.

In April and May 2016 the questionnaires on demographic characteristics and reproductive histories were sent by email to 256,543 female monitors aged 20–44 years old residing in Japan. The number of invitations was decided by Rakuten Research based on the expected response rate of the survey. The questionnaire consisted of two parts, i.e. eligibility check and the main questions. Out of 12,517 women who completed the questionnaire, 6,752 were eligible. Since it was also an interest to estimate the effect of age on TTP including the right-censored TTP (duration of trying to conceive without success)\(^21\), eligible women comprised those who were either parous (group A; \(n = 4,766\),
nulliparous and currently pregnant (group B; \(n = 305\)), or nulliparous, not pregnant, and with a partner (married or in other form) and not on contraception, i.e. at risk of conception (group C, \(n = 1,681\)). We included group C, because we needed to collect information on right-censored TTP, which is important to estimate association between age and TTP\textsuperscript{21}).

The analytic sample (\(n = 4,208\)) of the present study was parous women with first-born singleton. They were selected from the parous group (group A; \(n = 4,766\)) as shown in Figure 1. Participants whose data was deemed unreliable were excluded (Figure 1). The reasons to judge unreliable data included gestational ages of shorter than 22 or longer than 44 weeks, birth weight by gestational age being outside the commonly expected ranges (out of mean \(\pm 3SD\)), and mother’s BMI < 12 or \(\geq 50\) kg/m\(^2\). Participants whose first children were multiple births (\(n = 54\)) were also excluded because the rate of preterm birth among those with multiple pregnancy was very high according to the present data, which was not a focus of the present study. One participant who delivered a preterm baby at home was excluded, because in the questionnaire we asked whether membrane rupture and/or labor was present at the time of admission for delivery to judge the delivery was either spontaneous or indicated. All analyses were conducted using information on the first-born singleton children only to avoid possible confounding by mother’s parity.

We modified Harlow et al.’s\textsuperscript{19} definition to differentiate between spontaneous and indicated preterm birth. We asked the participants whether

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**Figure 1** Flow diagram for the selection of sample. A total of 12,517 women responded to the screening questionnaire, out of whom 5,765 were not eligible for the main questionnaire survey, because they did not fall into any of the eligibility group, i.e. A, B, or C. See the text for more detailed description.
the membrane rupture and/or labor was present at the time of admission for delivery. Indicated birth was defined in cases there was no rupture of membranes or labor at the time of admission, regardless of the route of delivery. In all other cases, i.e. presence of membrane rupture and/or labor at the time of admission, it was judged that the delivery process was initiated spontaneously. Preterm births that initiated spontaneously were categorized as spontaneous preterm births and all other preterm births were categorized as indicated preterm births. We believe self-report of the presence of membrane rupture and labor in the present study is reliable, because at pregnancy check-ups mothers are repeatedly taught to observe their labor timing and presence of membrane rupture very carefully as to judge when they should call and go to hospital or birthing center for delivery.

TTP was asked in the following question: “Please tell us about your condition when you became pregnant with your first child.” There were three answer choices: (1) I became pregnant despite using contraceptive methods, (2) I became pregnant as a result of discontinuing contraception, or (3) I had never used any contraceptive methods since I started dating my current partner. Only the respondents who conceived after discontinuing contraception, i.e. response (2), were asked to report their TTP. Those who conceived despite using contraception (1) or had never practiced contraception (3) were not asked to report the TTP values and were categorized as having “unknown TTP”. Gestational age information was elicited in the following way. Respondents were first asked “Do you remember each of your children’s gestational age at the time of birth?” If they chose “Yes”, then they were asked to provide the information. If “No”, they were asked if he or she was born on the due date. If the baby was not born on the due date, the respondents were then asked how many days ahead of or behind the due date. It is common for Japanese mothers that they remember well about the timing of their delivery, i.e. how many days ahead or behind due date, because they tend to become anxious and count days as approaching due date and that mothers tend to talk about the timing of delivery with their friends. On the other hand, many mothers do not remember exact gestational age, because they do not usually mention it in daily life.

Ethical approval for the survey was obtained from the Ethics Committee of the Graduate School of Medicine, The University of Tokyo (number: 10355–(1)). Informed consent was obtained from each participant upon starting of the online questionnaire survey.

1 Statistical analysis

Multinomial logistic regression analysis was performed separately for preterm birth outcome defined by two gestation cut-offs: at < 37 or at < 34 weeks. The two cut-offs were selected according to a previous Japanese study on preterm birth and infertility treatment\(^\text{14}\). In each model the outcome variable had 3 categories representing spontaneous preterm births, indicated preterm births, and term and post-term births (37–44 weeks of gestation). The explanatory variable was TTP (< 6 months, 6–11 months, 12+ months, unknown) (reference values are indicated in italic). The potential confounders that are known to be associated with the risk of preterm birth\(^\text{1,16,22}\) were adjusted for in the models, which include maternal age (< 20, 20–24,
Among a total of 4,208 singleton births, the number of spontaneous preterm births at < 34 weeks was 24 (0.6%), indicated preterm births at < 34 weeks was 9 (0.2%), spontaneous preterm births at < 37 weeks was 192 (4.6%), and indicated preterm births at < 37 weeks was 64 (1.5%) (Table 1). Mean (SD) maternal age was 29.1 (4.7) years old. The number of women who gave birth by vaginal delivery were 3,541 (84.1%), by caesarean section were 606 (14.4%) and by other ways were 61 (1.4%). The number of women who conceived naturally was 3,954 (94.0%) and those conceived as a result of ART were 254 (6.0%). Compared with women with term and post-term birth (median: 3.0 months; IQR: 1.0–12.0 months), women with spontaneous preterm birth at < 34 weeks (median: 12.0 months; IQR: 5.5–12.5 months) and those with indicated preterm birth at < 34 weeks (median: 12.0 months; IQR: 2.5–13.0 months) reported a longer TTP (Table 1).

Women who conceived following ART had significantly lower odds of indicated, but not spontaneous, preterm birth at < 37 weeks compared with women who conceived naturally (OR 0.11, 95% CI 0.02–0.83) (Table 2). Compared with women with TTP < 6 months, women with TTP 12+ months (OR 4.55, 95% CI 1.10–18.77) and with unknown TTP (OR 3.67, 95% CI 1.02–13.19) had significantly higher odds of spontaneous, but not indicated, preterm birth at < 34 weeks (Table 2). There was non-significant association between unknown TTP and spontaneous, but not indicated, preterm birth at < 37 weeks (OR 1.38, 95% CI 0.98–1.96) (Table 2). Results of sensitivity analysis (Table 3) revealed that the ORs did not deviate substantially, although the marginal association between unknown TTP and spontaneous preterm birth at < 37 weeks had disappeared.
Table 1  Basic characteristics and reproductive histories of the participants at the time of survey unless otherwise noted. Mean (SD), median (inter quantile range) or n (%).

| Characteristics                        | Total n = 4,208 (100%) | Preterm births at < 34 weeks | Preterm births at < 37 weeks | Term and post-term births |
|----------------------------------------|-------------------------|-------------------------------|------------------------------|----------------------------|
|                                         | n = 4208 (100%)         | Spontaneous n = 24 (0.6%)    | Indicated n = 9 (0.2%)       | Spontaneous n = 192 (4.6%) | Indicated n = 64 (1.5%)   | Term and post-term births n = 3,952 (93.9%) |
| Maternal age at delivery(years)         |                         |                               |                              |                            |                              |                              |
| 15-19                                   | 29.1 (4.7)              | 29.9 (4.0)                    | 32.9 (6.0)                   | 29.3 (4.6)                 | 31.5 (5.9)                   | 29.1 (4.7)                   |
| 20-24                                   | 625 (14.9%)             | 3 (12.5%)                     | 1 (11.1%)                    | 27 (14.1%)                 | 8 (12.5%)                    | 590 (14.9%)                  |
| 25-29                                   | 1,591 (37.8%)           | 8 (33.3%)                     | 2 (22.2%)                    | 78 (40.6%)                 | 16 (25.0%)                   | 1,497 (37.9%)                |
| 30-34                                   | 1,365 (32.4%)           | 11 (45.8%)                    | 1 (11.1%)                    | 55 (28.6%)                 | 17 (28.6%)                   | 1,293 (32.7%)                |
| 35-39                                   | 500 (11.9%)             | 2 (8.3%)                      | 5 (55.6%)                    | 29 (15.1%)                 | 17 (28.6%)                   | 454 (11.5%)                  |
| 40-44                                   | 71 (1.7%)               | 0 (0.0%)                      | 0 (0.0%)                     | 1 (0.5%)                   | 5 (7.8%)                     | 65 (1.6%)                   |
| Maternal height(cm)                    | 158.5 (5.5)             | 156.6 (11.5)                  | 161.7 (7.5)                  | 158.4 (7.2)                | 159.1 (5.6)                  | 158.5 (5.4)                  |
| Maternal weight(kg)                    | 53.0 (6.4)              | 53.0 (7.0)                    | 64.1 (7.5)                   | 52.8 (8.3)                 | 54.3 (8.4)                   | 52.9 (8.4)                  |
| Maternal BMI(kg/m²)                    | 21.1 (3.1)              | 22.6 (4.9)                    | 24.6 (3.4)                   | 21.1 (3.4)                 | 21.5 (3.4)                   | 21.1 (3.1)                  |
| Smoking history                         |                         |                               |                              |                            |                              |                              |
| Never                                  | 2,698 (64.1%)           | 12 (50.0%)                    | 6 (66.7%)                    | 119 (62.0%)                | 36 (56.3%)                   | 2,543 (64.3%)                |
| Former                                 | 936 (22.2%)             | 8 (33.3%)                     | 3 (33.3%)                    | 53 (27.6%)                 | 18 (28.1%)                   | 865 (21.9%)                  |
| Current                                | 574 (13.6%)             | 4 (16.7%)                     | 0 (0.0%)                     | 20 (10.4%)                 | 10 (15.6%)                   | 544 (13.8%)                  |
| Sex of the first child                  |                         |                               |                              |                            |                              |                              |
| Male                                    | 2,143 (50.9%)           | 10 (41.7%)                    | 3 (33.3%)                    | 118 (61.5%)                | 36 (56.3%)                   | 1,988 (50.3%)                |
| Female                                  | 2,065 (49.1%)           | 14 (58.3%)                    | 7 (66.7%)                    | 71 (38.5%)                 | 24 (38.5%)                   | 1,963 (49.7%)                |
| History of abortion                   |                         |                               |                              |                            |                              |                              |
| Never                                  | 3,654 (86.8%)           | 19 (79.2%)                    | 8 (88.9%)                    | 171 (90.9%)                | 51 (79.7%)                   | 3,432 (86.8%)                |
| Ever                                    | 554 (13.2%)             | 5 (20.8%)                     | 1 (11.1%)                    | 21 (10.9%)                 | 13 (20.3%)                   | 520 (13.2%)                  |
| History of stillbirth                 |                         |                               |                              |                            |                              |                              |
| Never                                  | 4,167 (99.0%)           | 22 (91.7%)                    | 8 (88.9%)                    | 188 (97.9%)                | 62 (96.9%)                   | 3,917 (99.1%)                |
| Ever                                    | 41 (1.0%)               | 2 (8.3%)                      | 1 (11.1%)                    | 4 (2.1%)                   | 2 (3.1%)                     | 35 (0.9%)                   |
| History of indicated abortion      |                         |                               |                              |                            |                              |                              |
| Never                                  | 3,838 (91.2%)           | 23 (95.8%)                    | 9 (100.0%)                   | 175 (91.7%)                | 56 (87.5%)                   | 3,606 (91.2%)                |
| Ever                                    | 370 (8.8%)              | 1 (4.2%)                      | 0 (0.0%)                     | 16 (8.3%)                  | 8 (12.5%)                    | 346 (8.8%)                  |
| History of Chlamydia infection        |                         |                               |                              |                            |                              |                              |
| Never                                  | 3,927 (93.3%)           | 23 (95.8%)                    | 8 (88.9%)                    | 182 (94.8%)                | 56 (87.5%)                   | 3,689 (93.3%)                |
| Ever                                    | 281 (6.7%)              | 1 (4.2%)                      | 1 (11.1%)                    | 10 (5.2%)                  | 8 (12.5%)                    | 263 (6.6%)                  |
| Delivery method                        |                         |                               |                              |                            |                              |                              |
| Vaginal delivery                      | 3,541 (84.1%)           | 13 (54.2%)                    | 1 (11.1%)                    | 152 (79.2%)                | 17 (28.6%)                   | 3,372 (85.3%)                |
| Caesarean section                     | 606 (14.4%)             | 11 (45.8%)                    | 8 (88.9%)                    | 40 (20.8%)                 | 46 (71.9%)                   | 520 (13.2%)                  |
| Other                                  | 61 (1.4%)               | 0 (0.0%)                      | 0 (0.0%)                     | 0 (0.0%)                   | 1 (1.6%)                     | 60 (1.5%)                   |
| Place of delivery                      |                         |                               |                              |                            |                              |                              |
| Hospital                               | 3,873 (92.0%)           | 24 (100.0%)                   | 8 (88.9%)                    | 180 (93.8%)                | 60 (93.8%)                   | 3,633 (91.9%)                |
| Clinic                                 | 251 (6.0%)              | 0 (0.0%)                      | 0 (0.0%)                     | 11 (5.7%)                  | 2 (3.1%)                     | 238 (6.0%)                  |
| Maternity home                         | 72 (1.7%)               | 0 (0.0%)                      | 1 (0.0%)                     | 1 (0.5%)                   | 2 (0.0%)                     | 69 (1.7%)                   |
| Home                                   | 4 (0.1%)                | 0 (0.0%)                      | 0 (0.0%)                     | 0 (0.0%)                   | 0 (0.0%)                     | 4 (0.1%)                    |
| Other                                  | 8 (0.2%)                | 0 (0.0%)                      | 0 (0.0%)                     | 0 (0.0%)                   | 0 (0.0%)                     | 8 (0.2%)                    |
Preterm births at < 34 weeks | Preterm births at < 37 weeks | Term and post-term births
--- | --- | ---
Total | n = 4,208 (100%) | n = 192 (4.6%) | n = 64 (1.5%) | n = 3,952 (93.9%)
Spontaneous | n = 24 (0.6%) | n = 5 (0.0%) | n = 6 (0.0%) | n = 1,016 (25.7%)
Indicated | n = 9 (0.2%) | n = 3 (33.3%) | n = 16 (25.0%) | n = 622 (15.7%)

### Academic background

| | Total | Spontaneous | Indicated |
|---|---|---|---|
| Junior high school | 101 (2.4%) | 0 (0.0%) | 0 (0.0%) |
| High school | 1,077 (25.6%) | 5 (0.0%) | 3 (33.3%) |
| Specialized/professional training college | 665 (15.8%) | 4 (16.7%) | 0 (0.0%) |
| Junior/technical college | 834 (19.8%) | 4 (16.7%) | 2 (22.2%) |
| University | 1,417 (33.7%) | 10 (41.7%) | 3 (33.3%) |
| Graduate school | 104 (2.5%) | 1 (4.2%) | 1 (11.1%) |
| Other | 10 (0.2%) | 0 (0.0%) | 0 (0.0%) |

### Types of employment

| | Total | Spontaneous | Indicated |
|---|---|---|---|
| Regular employee | 941 (22.4%) | 6 (25.0%) | 3 (33.3%) |
| Part-timer | 933 (22.2%) | 3 (12.5%) | 1 (11.1%) |
| Temporary or contract worker | 164 (3.9%) | 1 (4.2%) | 0 (0.0%) |
| Self-employed | 164 (3.9%) | 0 (0.0%) | 0 (0.0%) |
| Household worker | 1,805 (42.8%) | 13 (54.2%) | 3 (33.3%) |
| Unemployed | 189 (4.5%) | 1 (4.2%) | 2 (22.2%) |
| Student | 3 (0.1%) | 0 (0.0%) | 0 (0.0%) |
| Unknown | 9 (0.2%) | 0 (0.0%) | 0 (0.0%) |

### Household income (million yen)

| | Total | Spontaneous | Indicated |
|---|---|---|---|
| No income | 39 (0.9%) | 0 (0.0%) | 0 (0.0%) |
| < 2 | 171 (4.1%) | 0 (0.0%) | 0 (0.0%) |
| 2-3.9 | 761 (18.1%) | 4 (16.7%) | 4 (44.4%) |
| 4-5.9 | 1,261 (30.0%) | 4 (16.7%) | 2 (22.2%) |
| 6-7.9 | 839 (19.9%) | 8 (33.3%) | 1 (11.1%) |
| 8-9.9 | 410 (9.7%) | 3 (12.5%) | 1 (11.1%) |
| 10+ | 352 (8.4%) | 1 (4.2%) | 0 (0.0%) |
| Unknown | 375 (8.9%) | 4 (16.7%) | 1 (11.1%) |

### Types of pregnancy

| | Total | Spontaneous | Indicated |
|---|---|---|---|
| Natural pregnancy | 3,954 (94.0%) | 22 (91.7%) | 9 (100.0%) |
| Conceived by ART<sup>e</sup> | 254 (6.0%) | 2 (8.3%) | 0 (0.0%) |

### TTP (months)<sup>f</sup>

| | Total | Spontaneous | Indicated |
|---|---|---|---|
| < 6 months | 1,351 (32.1%) | 3 (12.5%) | 3 (33.3%) |
| 6-11 months | 364 (8.7%) | 2 (8.3%) | 0 (0.0%) |
| 12+ months | 609 (14.5%) | 6 (25.0%) | 4 (44.4%) |
| Unknown | 1,884 (44.8%) | 13 (54.2%) | 2 (22.2%) |

BMI, body mass index; TTP, time to pregnancy.

<sup>a</sup> For the first child.
<sup>b</sup> Maternal weight right before becoming pregnant with the first child.
<sup>c</sup> Maternal BMI right before becoming pregnant with the first child.
<sup>d</sup> Before the first childbirth.
<sup>e</sup> Getting pregnant by using ovulatory drugs, artificial insemination, in vitro fertilization and/or micro-insemination.
<sup>f</sup> TTP for pregnancy of the first child. TTP was known for n = 2,324 participants (n = 11 for spontaneous preterm births at < 34 weeks, n = 7 for indicated preterm births at < 34 weeks, n = 91 for spontaneous preterm births at < 37 weeks, n = 35 for indicated preterm births at < 37 weeks and n = 2,198 for term and post-term).
The proportions of preterm births at < 37 weeks by maternal age category among the first-born singletons were slightly higher among the respondents of the present survey (limited to births between 2007 and 2016) compared with those within the 15–19 age group (Figure 2a). Maternal ages at first birth were slightly higher among the respondents of the present survey (limited to births between 2007 and 2016) compared with those of the national sample (Figure 2b). The proportions of multiple births among the first-borns in the Internet survey and the vital statistics live birth data were 0.00% (n = 104 births) vs. 0.78% (n = 6,197,448) in 1985–1995, 1.73% (n = 1,330) vs. 1.25% (n = 6,159,115) in 1996–2006 and 1.09% (n = 2,849) vs. 1.18% (n = 3,995,005) in 2007–2016, respectively.

### IV Discussion

The present study showed that in comparison with women with a TTP of < 6 months, women with a TTP of 12 months or longer had significantly higher proportions of preterm births at < 34 weeks, with a TTP of 12 months or longer had significantly higher proportions of preterm births at < 34 weeks.
Table 3  Odds ratios and 95% confidence intervals for spontaneous and indicated preterm births at < 34 and < 37 weeks of gestational age in association with explanatory variables, limited to the babies born between 2007 and 2016 (n = 2,816) from the survey data.

| Explanatory variables                  | Preterm births at < 34 weeks | Preterm births at < 37 weeks |
|----------------------------------------|-----------------------------|-----------------------------|
|                                        | Spontaneous (n = 21) | Indicated (n = 8) | Spontaneous (n = 129) | Indicated (n = 48) |
|                                        | OR  95% CI     | OR  95% CI     | OR  95% CI     | OR  95% CI     |
| Maternal age (years) 25-29 (ref)       | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| 15-19                                  | NA NA          | NA NA          | NA NA          | NA NA          |
| 20-24                                  | 0.89 0.18-4.36| 5.29 0.31-91.00| 0.63 0.29-1.37| 0.77 0.17-3.53 |
| 30-34                                  | 0.86 0.32-2.27| 0.80 0.05-13.10| 0.63 0.41-0.97| 1.06 0.47-2.40 |
| 35-39                                  | 0.35 0.07-1.71| 9.60 1.08-85.27| 1.04 0.64-1.70| 3.21 1.46-7.05 |
| 40-44                                  | NA NA          | NA NA          | 0.26 0.03-1.90| 7.09 2.29-21.99|
| BMI (kg/m^2) 18.5-24.9 (ref) ^        | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| < 18.5                                 | 0.49 0.09-1.73| NA NA          | 1.09 0.69-1.72| 0.48 0.17-3.16 |
| 25.0+                                  | 0.32 0.04-2.41| 3.40 0.77-15.12| 0.63 0.29-1.37| 0.92 0.42-2.47 |
| Never smoke (ref)                      | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| Former smoking                         | 2.24 0.89-5.66| 1.64 0.36-7.39| 1.28 0.85-1.92| 1.34 0.70-2.55 |
| Current smoking                        | 1.35 0.29-6.36| NA NA          | 0.84 0.43-1.67| 0.68 0.30-2.31 |
| Male child                             | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| Female child                           | 1.47 0.61-3.52| 2.70 0.52-14.06| 0.63 0.44-0.91| 0.78 0.44-1.40 |
| Pregnant before conceiving the first child (ref): Never | 1.00 - 1.00 | 1.00 - 1.00 | 1.00 - 1.00 | 1.00 - 1.00 |
| Ever                                   | 1.07 0.39-2.98| 0.86 0.15-4.77| 0.85 0.53-1.34| 1.40 0.73-2.69 |
| Diagnosed with Chlamydia infection: Never (ref) | 1.00 - 1.00 | 1.00 - 1.00 | 1.00 - 1.00 | 1.00 - 1.00 |
| Ever                                   | NA NA          | 1.81 0.20-16.58| 0.44 0.16-1.21| 1.64 0.63-4.31 |
| Natural pregnancy (ref)                | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| Pregnancy by ART b                      | 1.27 0.25-5.46| NA NA          | 0.82 0.49-1.71| 0.12 0.02-0.88 |
| TTP < 6 months (ref) c                  | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    | 1.00 - 1.00    |
| 6-11 months                            | 2.69 0.44-16.26| NA NA          | 0.97 0.49-1.92| 0.19 0.03-1.49 |
| 12 months                              | 4.67 1.12-19.42| 4.23 0.73-24.64| 1.10 0.62-1.93| 1.61 0.75-3.46 |
| Unknown                                | 3.24 0.87-12.11| 0.69 0.09-5.15| 1.28 0.83-1.96| 0.87 0.43-1.76 |

CI, confidence interval; NA, not applicable; OR, odds ratio; TTP, time to pregnancy.

^ Maternal BMI right before becoming pregnant with the first child.

b Getting pregnant by using ovulatory drugs or artificial insemination or in vitro fertilization or micro-insemination.

c TTP for pregnancy of the first child. TTP was known for n = 1,702 participants (n = 11 for spontaneous preterm births at < 34 weeks, n = 6 for indicated preterm births at < 34 weeks, n = 72 for spontaneous preterm births at < 37 weeks, n = 30 for indicated preterm births at < 37 weeks and n = 1,600 for term and post-term).

Figure 2  (a) Proportions of preterm births at < 37 weeks by maternal age category and (b) proportions of births by maternal age category, among the first-born singletons born between 2007 and 2014 for the vital statistics live birth data and between 2007 and 2016 for the present survey data in Japan. Proportions were calculated separately using the vital statistics live birth data and the present survey data.
higher odds of spontaneous preterm birth at < 34 weeks of gestation. This was also observed in women with unknown TTP, but in the analysis restricted to the more recent data (i.e. 2007–2016), the association was not replicated. When preterm birth was defined at a longer cut-off of < 37 weeks, an association with the length of TTP was not observed.

This study is the first to suggest that a longer TTP was associated with spontaneous preterm birth. While previous studies have suggested an association between longer TTP and preterm birth, no distinction has been made between spontaneous and indicated preterm birth. It has been suggested previously that untreated (for infertility) women with a TTP of more than 1 year might have higher risk of preterm birth at < 34 and < 37 weeks compared with women with a TTP of 1 year or shorter; similarly, women whose TTP was longer than 12 months showed higher risk of preterm birth at < 37 weeks compared with women with a shorter TTP of ≤ 6 months. Another study has linked untreated women with a TTP of 7–12 months and 13–24 months to preterm birth at < 37 weeks in comparison with women with a TTP of ≤ 6 months. Wise and colleagues suggested that women with a TTP of 12+ menstrual cycles may have significantly higher risk of preterm birth at < 35 weeks compared with women with a TTP of < 3 cycles. A meta-analysis of 16 studies has estimated that women with long (> 12 months) TTP may have higher risk of preterm birth compared with women with short (12 months and shorter) TTP (OR: 1.31, CI: 1.21–1.42). While it is not directly comparable, we judge that our finding of the association between longer TTP and increased odds of preterm birth is similar to the findings of these previous studies in that they all reported that women with longer TTP were more likely to experience preterm delivery.

The mechanisms that underlie the association between preterm birth and long TTP are unclear despite the numerous studies that have provided evidence. Findings of the current study suggest that longer TTP is linked with increased rate of preterm birth through an increase in the rate of spontaneous preterm birth. It suggests that conditions that are commonly linked to indicated preterm birth, i.e. severe gestational diabetes, does not explain the observe association between longer TTP and preterm births, and that there may be other factors linking these two. Known risk factors for spontaneous preterm birth that were not adjusted in the present analysis include the history of genital infection, uterine anomaly, periodontal disease, and high levels of personal stress. Other risk factors such as the use of ART, cigarette smoking, pre-pregnancy underweight and overweight were however adjusted in the analysis. Future study is necessary to examine the possible contribution (confounding) of these unadjusted factors to the observed association between delayed conception and spontaneous preterm birth.

Women with unknown TTP had higher odds of spontaneous preterm birth compared with women with known TTP in the current research. Cooney and colleagues reported that the rates of preterm birth (at < 37 weeks) were higher among women with unknown TTP compared with women with known TTP (24% vs. 14%). They suspected that TTP errors might be more frequent among women with irregular menses or ovulatory dysfunction. However, ultrasonographic diagnosis is widely available in Japan and the precision of gestational age estimation is high, therefore we believe that the association between unknown TTP and spontaneous preterm birth observed in the present study may not be fully attributed to error in the estimation of gestational age.

The respondents of the survey had higher preterm birth rates and were older compared to
those in the vital statistics. This might be driven by women who were interested in the issues of reproductive health since they might be more likely to respond to the questionnaire. Another likely explanation is that the difference in maternal age structure might be related to the original age structure of the monitors maintained by the research company. In light of this, maternal age was included as a covariate for adjustment in the statistical model and thus, the age composition of our sample should not affect the estimated association between preterm birth and TTP.

Women who conceived following ART had significantly lower odds of indicated preterm birth at < 37 weeks compared with women who conceived naturally. It might be hypothesized that women who conceived with the use of ART were more health-conscious during the ART process and pregnancy, and hence were less likely to experience health issues that might require artificial discontinuation of pregnancy at earlier gestational ages. This hypothesis needs to be tested in future studies.

There are several limitations in this study. First, the participants were not randomly selected from a nationally representative sample and there were slight differences in age and rates of preterm births between the two populations as described above. Nevertheless, several previous studies have suggested the reliability of Internet-based survey. Bälter and colleagues\(^\text{20}\) compared the response rates of printed vs. internet questionnaires. Although the response rate was higher in printed questionnaire (64%) compared with internet questionnaire (51%), there were no differences in the distribution of age, BMI and the current smoking status and only small differences in sex, education and food habits. Second, this study examined the effect of risk factors on preterm birth in a cross-sectional manner; it did not investigate factors that might contribute to the temporal changes of preterm birth rates over time as it would require time-varying information. Relating to this point, we could not obtain information on variables that are associated with probability of conception, including frequency and timing of intercourse. Thus we cannot examine potential role of these variables in the observed association between delayed conception and preterm births. Third, as already mentioned above, some of the known risk factors for spontaneous preterm birth, i.e. SES, the history of genital infection, uterine anomaly, periodontal disease, and high levels of personal stress\(^\text{24}\), were not adjusted for in the present analysis.

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Conception delay and spontaneous and indicated preterm birth among primiparous women in Japan

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和文抄録

目的：受胎持ち時間が自然早産あるいは人工早産と関連するか否かを分析する。
方法：日本国内に居住する第1子が単胎児である20〜44歳の経産婦を対象として、横断調査を実施した。受胎持ち時間や出生時補助医療の利用を含む出産歴についての情報を、インターネット調査によって収集した。入院時に母親がすでに陣痛あるいは破水をみていた場合に自然分娩と定義した。多項ロジスティック回帰分析を用いて潜在的関連因子の影響を調整したうえで、34週および37週未満の自然および人工早産のオッズ比と95%信頼区間を推定した。
結果：分析に用いたサンプルは初産で単胎児を出産した4208人の母親である。年齢、出生時補助医療の利用、その他の潜在的関連因子を調整後も、受胎持ち時間が12か月以上だった女性は6か月未満の女性と比較して、34週未満の自然早産について高いオッズ比（4.55，95%信頼区間1.10〜18.77）を示した。しかし37週未満の自然早産についてはオッズ比1.07（95%信頼区間0.65〜1.75）であった。受胎持ち時間がわからないと回答した女性は、受胎持ち時間6か月未満の女性と比較して、34週未満および37週未満の自然早産のオッズ比（各3.67，95%信頼区間1.02〜13.19；1.38，95%信頼区間0.98〜1.96）が高かった。受胎持ち時間と人工早産の間には関連がみられなかった。
結論：受胎持ち時間の短い母親と比較して、受胎持ち時間の長い母親は自然早産を経験しやすい。