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Curvilinear relationship between age and assisted reproduction technique success: retrospective analyses of US National ART Surveillance System data from 2010–2014

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KEY MESSAGE
Following ∩–shaped curvilinear regressions with age, assisted reproduction success rates are lower in young and older ages. The age–driven decline in success rates begins before the age of 30 years and occurs at increasing rates. Women over 30 years should not delay assisted reproduction, if it is their only option.

A B S T R A C T

In assisted reproduction technique cycles using fresh autologous embryos, the pattern by which outcomes per started cycle (live birth and clinical pregnancy) and per clinical pregnancy (live birth and miscarriage) change with age was determined. A dataset was created with 488,351 cycles. Success rates changed with age following well-fitted, ∩–shaped curvilinear (quadratic, cubic, quartic) regressions. These rates increased steadily from age <24–28 years (P = 0.001; P = 0.02; P = 0.04; respectively) with positive slopes ($P \le 0.03$); live birth and pregnancy rates per cycle were lower in women aged <25 years versus women aged 25–28 years (P = 0.0002; P = 0.01, respectively), and declined steadily thereafter with negative slopes ($P < 0.0001$). The initial increase occurred at decreasing rates; subsequent decline occurred at increasing rates. Women aged <29 years with successful outcomes were older than those who were unsuccessful (P = 0.001; P = 0.04; P = 0.001; respectively); those with successful outcomes were younger in other age groups ($P < 0.0001$). Miscarriage followed similar but reverse ∪–shaped curvilinear regressions. Age–driven decline in success rates begins <30 years and occurs at increasing rates, suggesting that women >30 years old with infertility should not delay assisted reproduction, if it is their only option.

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'But in my opinion, all things in nature occur mathematically.'
René Descartes (mathematician, philosopher, scientist; 1596–1650).

Introduction

According to the 2011–2013 National Survey of Family Growth, 11% (almost 7 million) of the 61 million women aged 15–44 years in the USA had received an infertility service, and about 6% of married women had infertility problems (CDC, 2015a, 2016a). One of the most common treatment options available to help such women conceive is assisted reproductive technique treatment, available since 1981 in the USA (CDC, 2012a, 2013a, 2014a, 2015a, 2016a).

Different types of assisted reproduction techniques exist (IVF versus gamete intra-fallopian transfer versus zygote intrafallopian transfer), involving different sources of eggs (non-donor versus donor), and different states of eggs/embryos (fresh versus frozen–thawed) (CDC, 2012a, 2013a, 2014a, 2015a, 2016a). IVF is the most common type of assisted reproduction technique. IVF comprises conventional IVF and intracytoplamic sperm injection (ICSI), which are sometimes both carried out in the same IVF cycle. Of assisted reproduction technique cycles using fresh embryos from non-donor eggs in 2010–2014 in the USA, over 99% involved IVF, and 66–69% also involved ICSI (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b). Assisted reproduction technique cycles using 'fresh embryos from non-donor eggs' comprise about one-half of the assisted reproduction technique cycles in the USA, although they declined steadily from 68.5% in 2010 to 44.5% in 2014 (with 92,862 of 208,604 assisted reproduction technique cycles in 2014) (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b). The *Fertility Clinic Success Rate and Certification Act of 1992* in the USA mandates that clinics carrying out assisted reproduction technique procedures annually submit their data to Centers for Disease Control and Prevention (CDC); and that CDC annually publish success rates of those clinics as well as national summary of success rates, with the first report published in 1997 for 1995 (CDC, 2012a, 2013a, 2014a, 2015a, 2016a).

Fertility in women declines with age (Frank et al., 1994; Gindoff and Jewelewicz, 1986; Jansen, 1984; Lim and Tsakok, 1997; Navot et al., 1991; O'Connor et al., 1998; Speroff, 1994). It is well established that success rates in assisted reproduction technique cycles using fresh autologous embryos also decline with advancing age, with age being the most important factor, among others, determining those success rates (Cai et al., 2011; CDC, 2012b, 2013b, 2014b, 2015b, 2016b; Choi et al., 2013; Hunault et al., 2002; Nelson and Lawlor, 2011; Ottosen et al., 2007; Templeton et al., 1996; Vaegter et al., 2017; van Loendersloot et al., 2010, 2013, 2014). It is widely assumed that success rates in those assisted reproduction technique cycles initially remain relatively stable with age, and decline steadily after 30s or mid-30s (CDC, 2012b, 2013b, 2014b, 2015b, 2016b; HFEA, 2016). To take into account the adverse effect of advancing age, the annual reports of national assisted reproduction technique registries break down success rates in those assisted reproduction technique cycles into age groups, e.g., in CDC's annual assisted reproduction technique reports, into age groups of less than 35 years, 35–37 years, 38–40 years, 41–42 years, 43–44 years and over 44 years (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b), and in Human Fertilisation and Embryology Authority (HFEA) reports, into age groups of 18–34, 35–37, 38–39, 40–42, 43–44 and over 44 years (HFEA, 2016).

Because age is the most important factor determining assisted reproduction technique success rates, it is also widely used (along with other factors) to predict success rates (Cai et al., 2011; Choi et al., 2013; Hunault et al., 2002; Nelson and Lawlor, 2011; Ottosen et al., 2007; Templeton et al., 1996; van Loendersloot et al., 2010, 2013, 2014; Vaegter et al., 2017). The pattern of (and the fitted mathematical model for) the change in assisted reproduction technique success rates with age, particularly in the population, is unknown. Therefore, the objective of this analysis was to determine the pattern of change in assisted reproduction technique success rates with age in cycles using fresh autologous embryos, and to develop a fitted mathematical model for this pattern. For this purpose, outcomes of assisted reproduction techniques per started cycle (live birth and clinical pregnancy) and outcomes per clinical pregnancy (live birth and miscarriage), in an 'accessible population' were studied (National ART Surveillance System [NASS] data from 2010–2014).

Materials and methods

Population and source of data

Centers for Disease Control and Prevention is able and willing to provide data from the National ART Surveillance System (NASS) to independent scientists. Therefore, de-identified raw data (with authorization to submit for publication) from CDC for years 2010–2014 on 488,351 assisted reproduction technique cycles using fresh embryos from non-donor eggs were obtained (CDC, 2016c). Of those assisted reproduction technique cycles, over 99% involved IVF, and 66–69% also involved ICSI (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b). The raw data consisted of the numbers of assisted reproduction technique cycles that started (including those that were subsequently cancelled) and the numbers of those cycles that resulted in clinical pregnancy and in live birth for every age of women (CDC, 2016c). Using the raw data, a dataset was created with 488,351 actual 'observations', with each 'observation' being an assisted reproduction technique cycle. Outcomes per started cycle (live birth and clinical pregnancy) and outcomes per clinical pregnancy (live birth and miscarriage) were analysed. Age is defined as age in years at cycle start. Cycle start is defined by NASS as the start of ovarian stimulation by medication in stimulated cycles, or as the start of ovarian monitoring (by ultrasound or blood tests) in unstimulated cycles (CDC, 2012b, 2013b, 2014b, 2015b, 2016b), with unstimulated cycles comprising less than 1–2% of those cycles between 2010–2014 (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b). Clinical pregnancy is defined by NASS as presence of an ultrasonographically detected gestational sac in the uterus (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b). Of the clinical pregnancies in 2010–2014, annually 17.9–18.3% resulted in non-occurrence of a live birth (15.8–16.2% in 'miscarriage,' and 2.0–2.3% either in 'stillbirth,' 'induced abortion' or 'unknown') (Figure 10 in CDC, 2012b, 2013b, 2014b, 2015b, 2016b). Therefore, most (87–89%) no live births in clinical pregnancies, i.e., 15.8–16.2 percentage points of 17.9–18.3%, were caused by miscarriage. Therefore, non-occurrence of a live birth per clinical pregnancy was treated, and statistically analysed, in this study as 'miscarriage per clinical pregnancy.' As mean rates of clinical pregnancy and live birth per started cycle had already been previously published by CDC for age groups

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(CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b), and for each age (Figure 14 in CDC, 2012b, 2013b, 2014b, 2015b, 2016b), Institutional Review Board approval was not needed.

Statistical analyses

Fitted curvilinear regression models (linear, quadratic, cubic and quartic, i.e., polynomial equations of the first, second, third and fourth degree, respectively) between each assisted reproduction technique outcome and age, for probability for occurrence of each cycle outcome, were developed by least squares analysis of variance using the general linear models procedure of SAS software (version 7; SAS Institute Inc., USA). How rapidly an assisted reproduction technique outcome predicted by quadratic, cubic and quartic regression models changes at every age, i.e., the instantaneous rate of change (or the 'instantaneous slope') at every age, and how this 'instantaneous slope' also changes with age, were determined by calculating the 'derivative' of each predicted assisted reproduction technique outcome at every age.

As data indicated that the success rates increased steadily with age until the age of 28 years, and declined steadily thereafter, fitted linear regression models were also developed within age groups of <29, 29–34, 35–37, 38–40, 41–42 and 43–44 by analysis of regression using the REG procedure of SAS as well as by least squares analysis of variance using the general linear models procedure of SAS, both of which yielded same results. Whether the linear regression slope within each age group was significantly different from zero (as indicator of whether there was indeed a significant and steady increase/decline within each age group) was also determined by the same analyses. These age groups correspond to those in CDC's annual assisted reproduction technique Reports (CDC, 2012a, 2012b, 2013a, 2013b, 2014a, 2014b, 2015a, 2015b, 2016a, 2016b), except that the age group of younger than 35 years was further broken down in our study into age groups of younger than 29 years and 29–34 years for the aforementioned reason.

We also compared assisted reproduction technique outcomes among individual ages and among aforementioned age groups (as well as after further splitting age group of <29 year into <25 years and 25–28 years) by least squares analysis of variance using the general linear models procedure of SAS. Within age groups, we also compared age of women between cycles that resulted in successful assisted reproduction technique outcomes and those that did not by least squares analysis of variance using the general linear models procedure of SAS. To determine the significance of correlation between occurrence of each assisted reproduction technique outcome and age, Pearson's correlation coefficients were calculated using the CORR procedure of SAS. $P < 0.05$ was considered to be significant.

Results

Numbers of assisted reproduction technique cycles that resulted in outcomes are shown in **Supplementary Table S1**.

Initial, steady increase in success rates followed by steady decline: adverse effect of very young and older ages

Live birth per started cycle increased steadily in women aged less than 24 years to the age of 28 years ($P = 0.001$), and declined steadily thereafter (**Figure 1A**). During the period of subsequent steady decline, live birth per started cycle at the age of 28 years was higher than those at every age thereafter ($P = 0.03$ versus 29 years; $P < 0.0001$ for others) (**Figure 1A**). Starting at the age of 29 years, live birth per started cycle at every age was also lower than that at the preceding age ($P < 0.03$ for age 28 years versus 29 years, 29 years versus 30 years, and 44 years versus over 44 years; $P < 0.0001$ for others), except for age 30 years versus 31 years (**Figure 1A**). Other success rates, i.e., pregnancy per cycle and live birth per pregnancy, also followed patterns similar to that described above, by increasing steadily from ages younger than 24 years to age 28 years ($P = 0.02$ and $P = 0.04$, respectively), and by declining steadily thereafter (**Figure 1B and 1C**). Conversely, miscarriage per pregnancy declined steadily from ages younger than 24 years to age 28 years ($P = 0.04$), and increased steadily thereafter (**Figure 1D**). During the period of subsequent steady increase, miscarriage at age 28 years was lower than those at every age thereafter ($P < 0.05$ versus age 29 years, 30 and 31 years; $P < 0.0001$ for others) (**Figure 1D**). Starting at age 29 years, miscarriage at most ages was also higher than that at the preceding age ($P < 0.03$) (**Figure 1D**).

Agreeing with the steady and significant increase with age among women younger than 29 years, both live birth and pregnancy rates per started cycle were lower in age group of women aged younger than 25 years than in women aged 25–28 years ($P = 0.0002$ and $P = 0.01$, respectively) (**Figure 2A and 2B**). After the age group of 25–28 years, success rate in every age group was lower than that in the preceding age group ($P < 0.0001$) (**Figure 2A–2C**) (**Supplementary Table S2**). Conversely, after the ages of 25–28 years, miscarriage per pregnancy in every age group was higher than that in the preceding age group ($P < 0.0001$) (**Figure 2D**) (**Supplementary Table S2**).

Success rates change with age in well-defined curvilinear regressions

Age was negatively correlated with success rates (live birth and pregnancy per started cycle, and live birth per pregnancy; $r = -0.23$, $r = -0.25$, and $r = -0.19$, respectively; $P < 0.0001$), and positively correlated with miscarriage per pregnancy ($r = 0.19$; $P < 0.0001$). The correlation coefficients, however, were rather low because of the curvilinear nature of the regressions. Similarly, although a significant ($P < 0.0001$) linear regression was observed between each assisted reproduction technique outcome and age (negative for success rates, and positive for miscarriage), they were not well-fitted in predicting observed means owing to the curvilinear nature of the regressions (**Supplementary Table S3**) (**Supplementary Figure S1**).

Success rates changed with age following well-fitted, ∩-shaped curvilinear regressions (for live birth per started cycle and per pregnancy, $P < 0.0001$ for quadratic, cubic and quartic; for pregnancy per started cycle, $P < 0.0001$, $P = 0.06$ and $P = 0.01$ for quadratic, cubic and quartic, respectively) (**Figure 1A–1C**) (**Supplementary Table S3**). Conversely, miscarriage per pregnancy also changed with age following well-fitted, ∪-shaped curvilinear (quadratic, cubic and quartic) regressions ($P < 0.0001$) (**Figure 1D**) (**Supplementary Table S3**).

Outcome rates predicted by those three well-fitted curvilinear regression models were almost identical to observed means (**Figure 1A–1D**), as, when validated, they accurately predicted the observed means within two percentage points (**Figure 1A and 1B**) or mostly within three percentage points (**Figure 1C and 1D**). Accordingly, those three well-fitted curvilinear regression models are also almost identical to one another, as they also overlap only within two to three percentage points (**Figure 1A–1D**). To illustrate how those

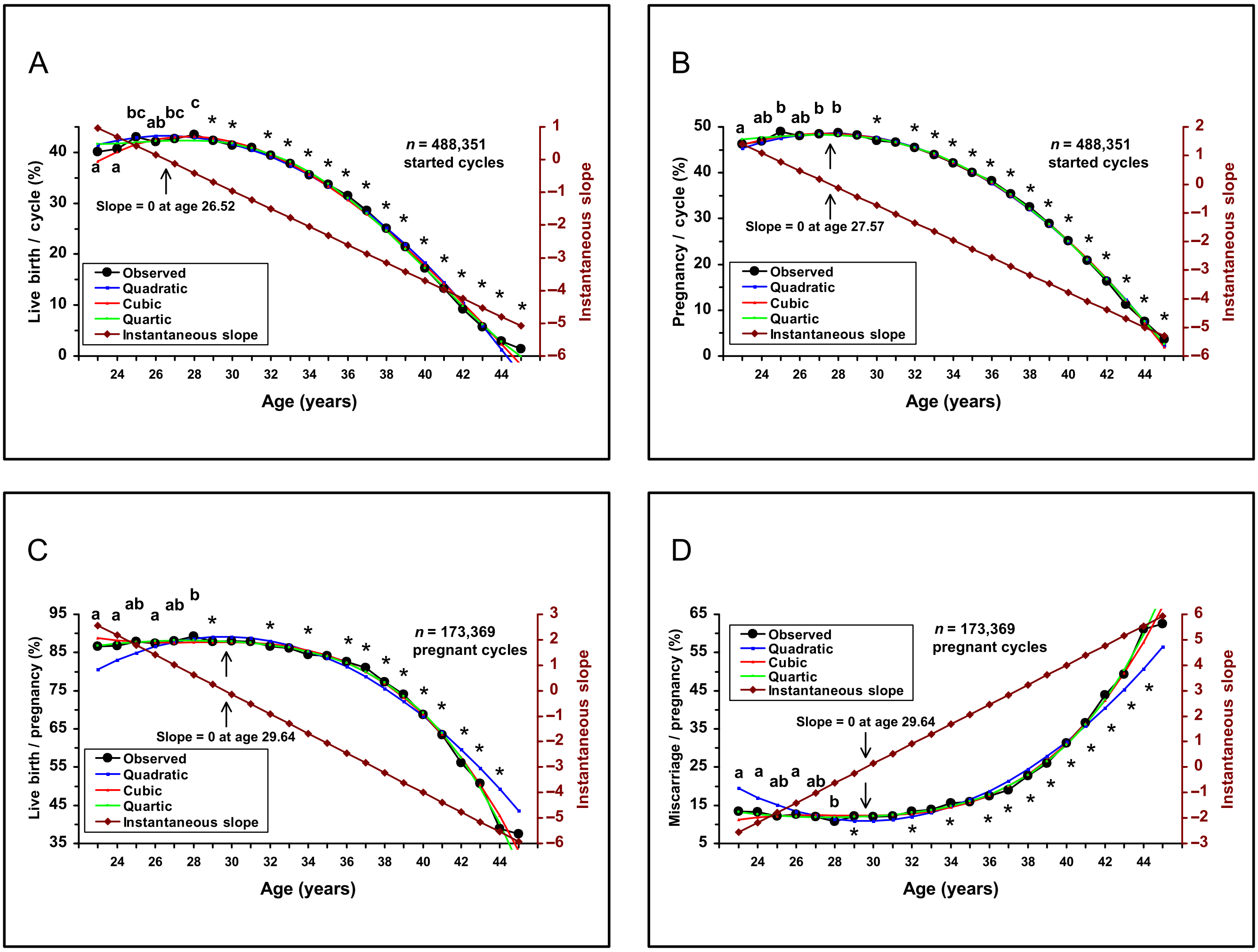

Figure 1 – Assisted reproduction technique outcomes as affected by age. Outcomes predicted by fitted curvilinear regression models are superimposed on observed rates. (A, C, D) $P < 0.0001$ for quadratic, cubic and quartic; (B) $P < 0.0001$, $P = 0.06$ and $P = 0.01$ for quadratic, cubic and quartic, respectively), along with their quadratic instantaneous slopes (rate of change). (A–D) Before the age of 29 years, means lacking a common letter differed ($P < 0.05$, $P < 0.04$, $P < 0.05$, $P < 0.05$ in A–D, respectively). (A–C) Success rates increased ($P = 0.001$, $P = 0.02$, $P = 0.04$, respectively) until the age of 28 years, and declined thereafter. Starting at the age of 29 years, means at almost every age (A, B) or at most ages (C) were lower than that at the preceding age ($P < 0.03$, $P < 0.01$, $P < 0.03$, respectively; indicated by an *). Predicted success rates initially increased at decreasing rates, and declined thereafter at increasing rates. (D) Miscarriage declined ($P = 0.04$) until the age of 28 years, and increased thereafter. Starting at the age of 29 years, means at most ages were higher than that at the preceding age ($P < 0.03$; indicated by an *). Predicted miscarriage rates initially declined at decreasing rates, and increased thereafter at increasing rates. (A–D) An instantaneous zero slope denoted by arrows indicates that when a predicted outcome on the quadratic regression line reaches its maximum (A-C) or minimum (D) value, its derivative (instantaneous slope) equals zero. Ages 23 and 45 years on X-axes represent ages less than 24 years and over 44 years, respectively.

three well-fitted curvilinear regression models differ from one another within each assisted reproduction technique outcome, outcomes predicted by those models were extended to hypothetical ages (**Figure 3A–3D**), showing that those models overlap between ages 23 and 45 years, hence, predicting outcomes, accurately and equally, only between those two ages.

Well-fitted curvilinear (quadratic, cubic and quartic) regression equations are given here only for live birth per started cycle. For other outcomes, only the quadratic regression equations are given here; all curvilinear regression equations are given in **Supplementary Table S3**. Quadratic, cubic and quartic regression equations for live birth per started cycle (LB/C) are, respectively:

$$\text{LB/C} = (-53.21944291) + (7.27532642 \times \text{age}) + (-0.13718085 \times \text{age}^2) + \varepsilon;$$

$$\text{LB/C} = (-190.521704) + (19.5054647 \times \text{age}) + (-0.4946022 \times \text{age}^2) + (0.00343 \times \text{age}^3) + \varepsilon;$$

$$\text{LB/C} = (550.3961082) + (-69.8458045 \times \text{age}) + (3.4899734 \times \text{age}^2) + (-0.0744934 \times \text{age}^3) + (0.0005642 \times \text{age}^4) + \varepsilon;$$

where LB/C is the per cent probability for occurrence of live birth per started cycle; age is the age of woman; and ε is the random error.

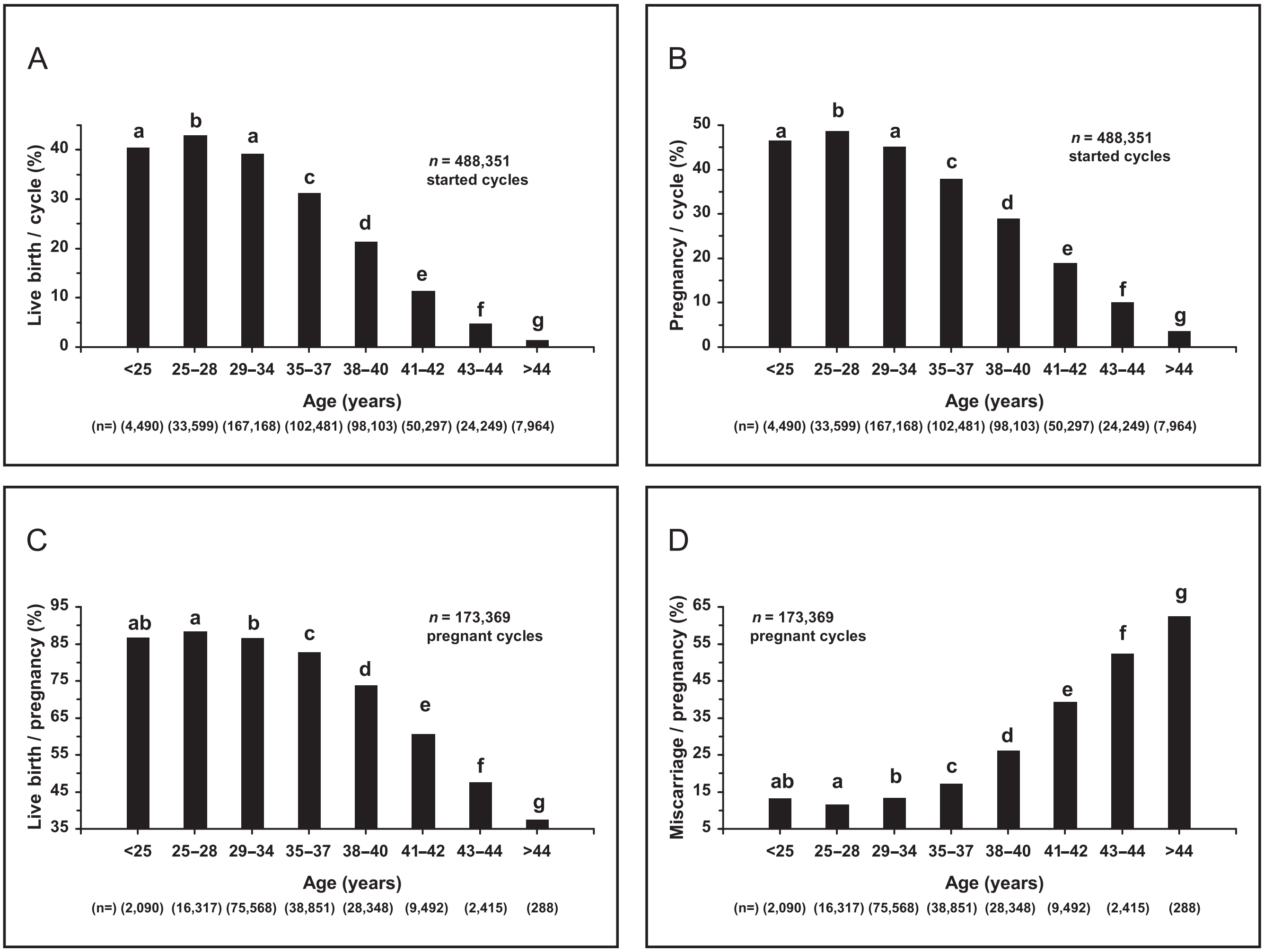

Figure 2 – Assisted reproduction technique outcomes in age groups. Means lacking a common letter differed: (A) $P = 0.0002$ for women aged less than 25 years versus women aged 25–28 years; $P < 0.0001$ for others; (B) $P = 0.01$ for women aged less than 25 years versus 25–28; $P < 0.0001$ for others; (C and D) $P < 0.0001$. Numbers in parentheses below age groups are numbers of cycles.

Quadratic regression equations for pregnancy per started cycle (PR/C), live birth per pregnancy (LB/P), and miscarriage per pregnancy (MC/P) are, respectively:

$$PR/C = (-67.00298871) + (8.38453808 \times age) + (-0.15208084 \times age^2) + \varepsilon;$$

$$LB/P = (-80.41453181) + (11.43783459 \times age) + (-0.19293939 \times age^2) + \varepsilon;$$

$$MC/P = (180.4145318) + (-11.4378346 \times age) + (0.1929394 \times age^2) + \varepsilon.$$

Success rates: initial increase at decreasing rates, and subsequent decline at increasing rates (instantaneous slopes)

Because assisted reproduction technique outcomes changed with age in well-fitted curvilinear regressions, the pattern of their change exhibited, by definition, the properties of curvilinear regressions. On a curvilinear regression line, the 'instantaneous slope' (instantaneous rate of change) at a given point on the curvilinear regression line is the slope of the straight line tangent to the curvilinear regression line at that point (represented in **Supplementary Figure S2**), and is called the 'derivative' of the dependent variable (or response, e.g., assisted reproduction technique outcome rate) for a given independent variable (or predictor, e.g., age). The 'instantaneous slope' of an assisted reproduction technique outcome at a given age indicates how rapidly outcome instantaneously changes at that age (i.e., percentage–point change in outcome rate). In a curvilinear regression line, the 'instantaneous slope' decreases or increases continuously (in contrast to a constant slope in a simple linear regression line).

Instantaneous slope (derivative) functions of assisted reproduction technique outcomes predicted by curvilinear regression models are given below (for the sake of simplicity, only for the quadratic regression models), which were used to generate 'instantaneous slopes' values in **Figure 1**. As reported earlier, the quadratic regression function of predicted live birth per started cycle (LB/C) with age is:

$$LB/C = (-53.21944291) + (7.27532642 \times age) + (-0.13718085 \times age^2)$$

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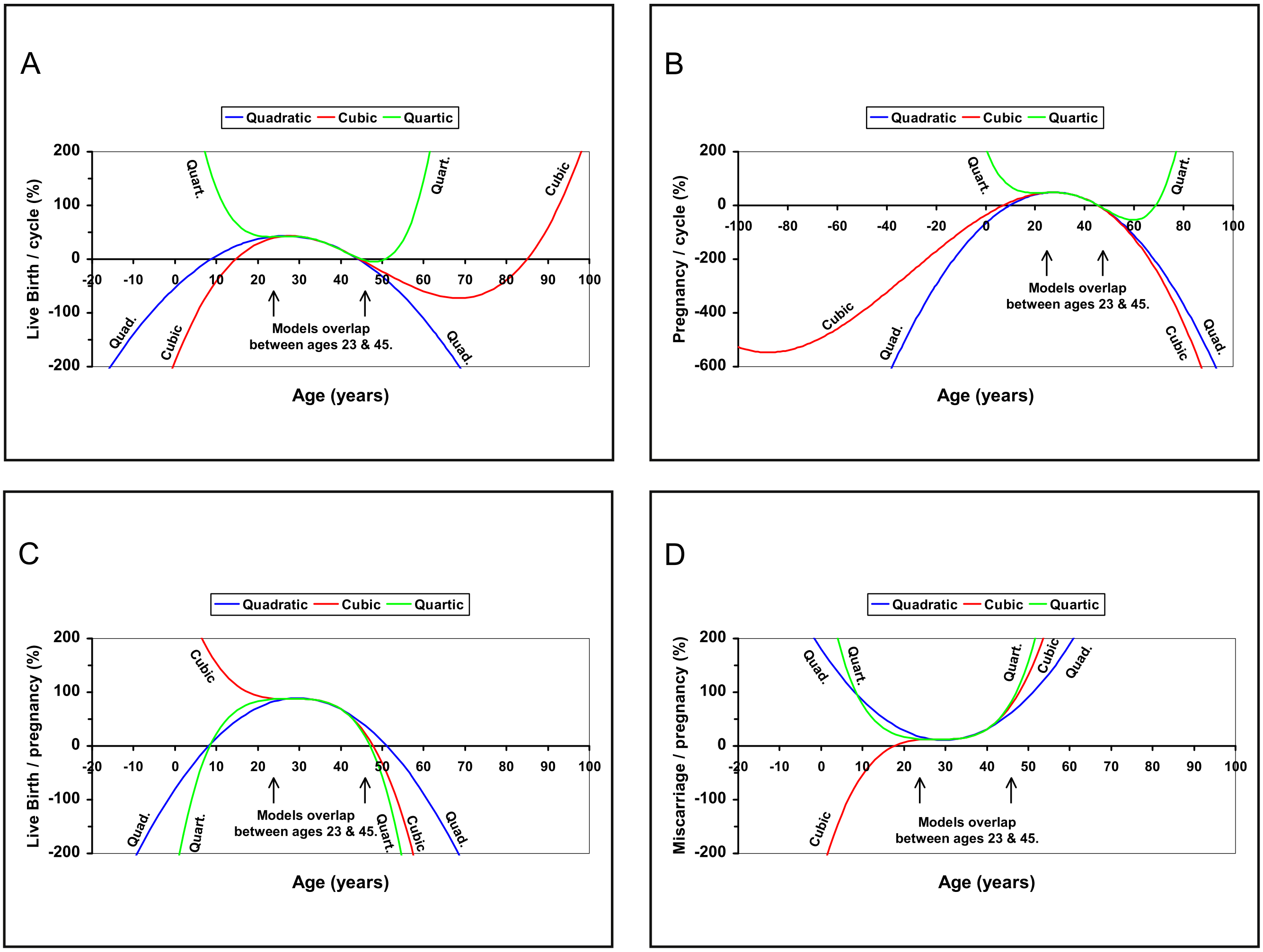

Figure 3 – Assisted reproduction technique outcomes predicted by fitted curvilinear regression models are extended to hypothetical ages, showing that those models overlap between the ages of 23 years and 45 years, thus equally predicting outcomes between those ages.

Therefore, the derivative (instantaneous slope) function of the above quadratic regression function of the predicted LB/C at a given age is:

$$d(LB/C)/d(age) = (7.27532642) + (2 \times -0.13718085 \times age) = (7.27532642) + (-0.2743617 \times age).$$

Similarly, the derivative (instantaneous slope) functions of the previously reported quadratic regression functions of the other three predicted assisted reproduction technique outcomes at a given age are:

$$d(PR/C)/d(age) = (8.38453808) + (-0.30416168 \times age)$$

$$d(LB/P)/d(age) = (11.43783459) + (-0.38587878 \times age)$$

$$d(MC/P)/d(age) = (-11.4378346) + (0.3858788 \times age).$$

Using the above instantaneous slope functions of assisted reproduction technique outcomes predicted by quadratic regression models, the instantaneous slopes of those predicted outcomes at each age were determined (Figure 1). As shown in Figure 1A–1C, predicted success rates initially increased at decreasing rates, i.e., with positive slopes decreasing in magnitude, or with decreasing positive slopes; reached their maximum values at about age 28 years, with zero instantaneous slopes; and declined thereafter at increasing rates, i.e., with negative slopes increasing in magnitude, or with decreasing negative slopes. Conversely, as shown in Figure 1D, predicted miscarriage rate per pregnancy initially declined at decreasing rates; reached its minimum value at about age 28 years, with a zero instantaneous slope; and increased thereafter at increasing rates.

The 'age' at which each predicted assisted reproduction technique outcome reached its maximum or minimum value with a zero instantaneous slope (Figure 1) was calculated by solving the 'age' in the derivative function equation of that predicted assisted reproduction technique outcome when the derivative equals zero, e.g., for predicted LB/C, by solving the 'age' in the derivative function equation:

$$0 = (7.27532642) + (-0.2743617 \times age).$$

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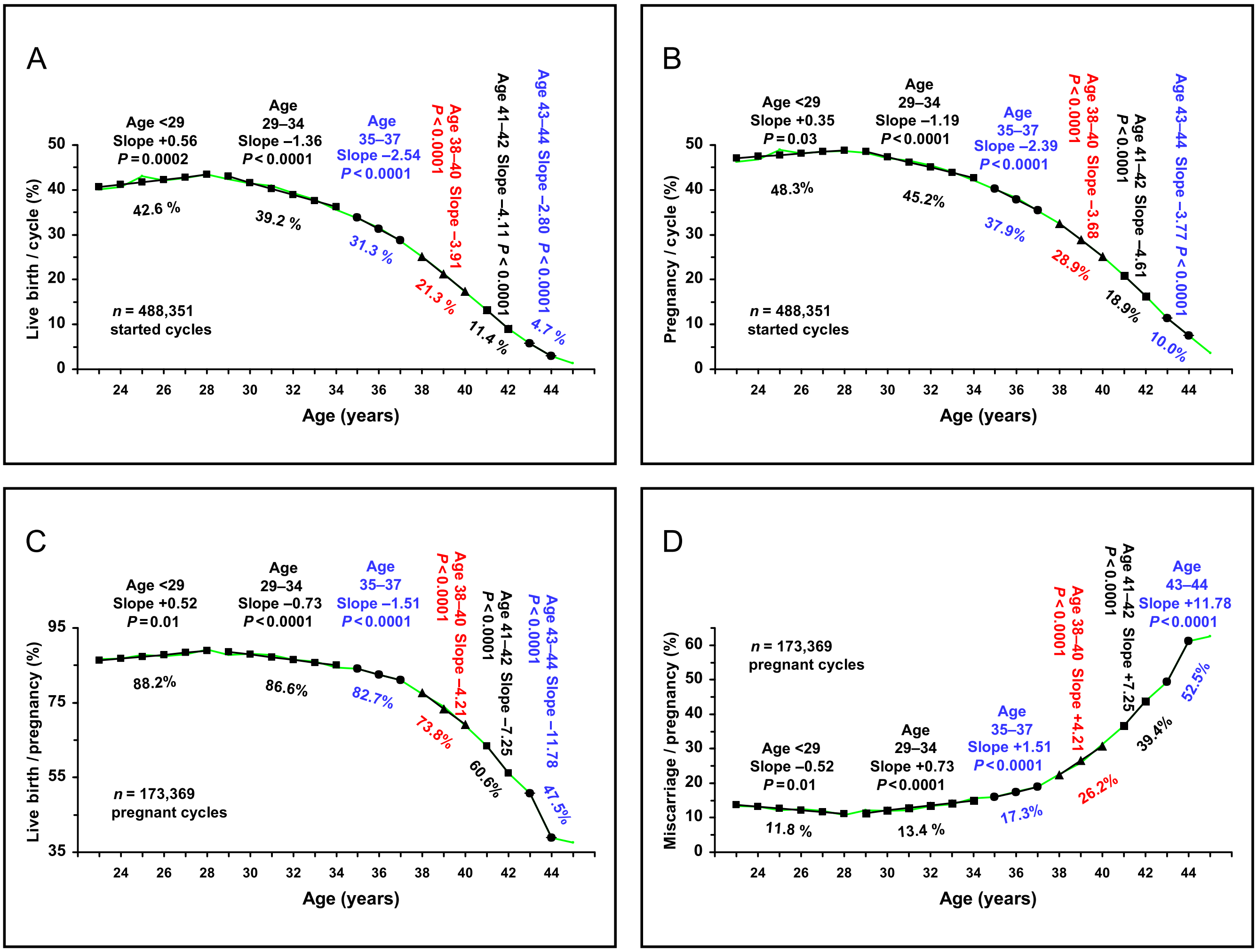

Figure 4 – Assisted reproduction technique outcomes predicted by linear regression models significantly ($P < 0.0001$) fitted within age groups (black lines), superimposed on observed rates (continuous green line). (A–C) Slope was significantly higher than zero in women aged less than 29 years. In subsequent age groups, it was significantly lower than zero, increasing in magnitude except in women aged between 43 and 44 years in A and B. (D) Slope was significantly lower than zero in women younger than 29 years. In subsequent age groups, it was significantly higher than zero, increasing in magnitude. (A–D) Percentages are mean rates in age groups; they differ among all age groups ($P < 0.0001$). Ages 23 and 45 years on X-axes represent ages less than 24 years and more than 44 years, respectively. Values of slopes are rounded up; their full values are given in Supplementary Table S4.

Therefore, for example, the 'age' at which the predicted LB/C reached its maximum value with a zero instantaneous slope was 26.52, as:

$$\text{Age} = (0 - 7.27532642)/{-0.2743617} = 26.52.$$

Change in success rates within age groups (slopes within age groups)

Fitted linear regression models within age groups are shown in **Figure 4** (equations given in **Supplementary Table S4**). The linear regression models within age groups, when validated, accurately predicted the observed means within 0.8 percentage point (except within 1.3 percentage point for age 25 for live birth and pregnancy per started cycle) (**Figure 4**). Each success rate increased steadily within age younger than 29 years with a positive slope higher than zero ($P \leq 0.03$), and declined steadily within subsequent age groups with negative slopes lower than zero ($P < 0.0001$) (**Figure 4A–4C**) (**Supplementary Table S2**), with the negative slope within each age group also being lower than that within the preceding age group (**Figure 4A–4C**) (**Supplementary Table S2**) except among women aged 43–44 years in **Figure 4A and 4B**). Agreeing with positive slopes among women aged younger than 29 years, women who had successful assisted reproduction technique outcomes were older than those who had unsuccessful outcomes (P = 0.001, P = 0.04, and P = 0.001, respectively) (**Tables 1–3**). Also agreeing with negative slopes within each subsequent age group (in age ≥29 years), women who had unsuccessful assisted reproduction technique outcomes were older than those who had successful outcomes ($P <$ 0.0001) (**Tables 1–3**). Conversely, miscarriage per pregnancy declined steadily within age younger than 29 years with a negative

Table 1 – Comparison of ages between women who had live birth and those who did not per started cycle using fresh autologous embryos.

Age group (years)	Age[a] (years) (mean ± SD)			
	Live birth per cycle	No–live birth per cycle	*P*-value	Overall
<29	26.61 ± 1.48 (16,229)	26.56 ± 1.51 (21,860)	0.001	26.58 ± 1.50 (38,089)
29–34	31.72 ± 1.65 (65,468)	31.88 ± 1.65 (101,700)	<0.0001	31.82 ± 1.65 (167,168)
35–37	35.92 ± 0.81 (32,114)	36.00 ± 0.82 (70,367)	<0.0001	35.98 ± 0.82 (102,481)
38–40	38.86 ± 0.80 (20,932)	39.01 ± 0.81 (77,171)	<0.0001	38.98 ± 0.81 (98,103)
41–42	41.35 ± 0.48 (5755)	41.45 ± 0.50 (44,542)	<0.0001	41.44 ± 0.50 (50,297)
43–44	43.22 ± 0.42 (1146)	43.37 ± 0.48 (23,103)	<0.0001	43.36 ± 0.48 (24,249)
>44[b]	– (108)	– (7856)	–	– (7964)
Overall	33.64 ± 4.19 (141,752)	36.26 ± 4.81 (346,599)	<0.0001	35.50 ± 4.79 (488,351)

[a] Numbers in parentheses are numbers of started assisted reproduction technique cycles.
[b] Comparison of ages between the two groups was not conducted among women aged over 44 years, as data in women aged over 44 years were pooled, as 7964 cycles constituted a tiny fraction (1.6%) of 488,351 started cycles.

Table 2 – Comparison of ages between women who got pregnant and those who did not per started cycle using fresh autologous embryos.

Age group (years)	Age[a] (years) (mean ± SD)			
	Pregnant per cycle	Not pregnant per cycle	*P*-value	Overall
<29	26.60 ± 1.49 (18,407)	26.56 ± 1.51 (19,682)	0.04	26.58 ± 1.50 (38,089)
29–34	31.72 ± 1.65 (75,568)	31.88 ± 1.65 (91,600)	<0.0001	31.82 ± 1.65 (167,168)
35–37	35.93 ± 0.81 (38,851)	36.00 ± 0.82 (63,630)	<0.0001	35.98 ± 0.82 (102,481)
38–40	38.90 ± 0.80 (28,348)	39.02 ± 0.81 (69,755)	<0.0001	38.98 ± 0.81 (98,103)
41–42	41.38 ± 0.49 (9492)	41.46 ± 0.50 (40,805)	<0.0001	41.44 ± 0.50 (50,297)
43–44	43.27 ± 0.44 (2415)	43.37 ± 0.48 (21,834)	<0.0001	43.36 ± 0.48 (24,249)
>44[b]	– (288)	– (7676)	–	– (7964)
Overall	34.02 ± 4.34 (173,369)	36.32 ± 4.82 (314,982)	<0.0001	35.50 ± 4.79 (488,351)

[a] Numbers in parentheses are numbers of started assisted reproduction technique cycles.
[b] Comparison of ages between the two groups was not conducted among women aged over 44 years, as data in women aged over 44 years were pooled, as 7964 cycles constituted a tiny fraction (1.6%) of 488,351 started cycles.

Table 3 – Comparison of ages between women who had live birth and those who did not, i.e., who had miscarriage, per pregnancy using fresh autologous embryos.

Age group (years)	Age[a] (years) (mean ± SD)			
	Live birth per pregnancy	Miscarriage per pregnancy	*P*-value	Overall
<29	26.61 ± 1.48 (16,229)	26.50 ± 1.51 (2178)	0.001	26.60 ± 1.49 (18,407)
29–34	31.72 ± 1.65 (65,468)	31.89 ± 1.66 (10,100)	<0.0001	31.75 ± 1.65 (75,568)
35–37	35.92 ± 0.81 (32,114)	35.99 ± 0.81 (6737)	<0.0001	35.93 ± 0.81 (38,851)
38–40	38.86 ± 0.80 (20,932)	39.00 ± 0.81 (7416)	<0.0001	38.90 ± 0.80 (28,348)
41–42	41.35 ± 0.48 (5755)	41.43 ± 0.49 (3737)	<0.0001	41.38 ± 0.49 (9492)
43–44	43.22 ± 0.42 (1146)	43.32 ± 0.47 (1269)	<0.0001	43.27 ± 0.44 (2415)
>44[b]	– (108)	– (180)	–	– (288)
Overall	33.64 ± 4.19 (141,752)	35.72 ± 4.59 (31,617)	<0.0001	34.02 ± 4.34 (173,369)

[a] Numbers in parentheses are numbers of assisted reproduction technique cycles with pregnancies.
[b] Comparison of ages between the two groups was not conducted among women aged over 44 years, as data in women aged over 44 years were pooled, as 288 cycles constituted a tiny fraction (0.2%) of 173,369 pregnant cycles.

slope lower than zero (P = 0.01), and increased steadily within subsequent age groups with positive slopes higher than zero (P < 0.0001), with the positive slope within each age group also being higher than that within the preceding age group (**Figure 4D**) (**Supplementary Table S2**).

Discussion

Assisted reproduction technique outcomes in 488,351 cycles using fresh autologous embryos from the NASS data from 2010–2014 were retrospectively analysed. With NASS data covering 97–98% of all assisted reproduction technique cycles conducted in the USA between 2010 and 2014 (CDC, 2012a, 2013a, 2014a, 2015a, 2016a), this study was conducted on an 'accessible population' rather than a 'sample' representing the 'population.' Therefore, this study assures the most reliable inferences about this population regarding the pattern of change in assisted reproduction technique success rates with age.

Assisted reproduction technique success rates in cycles using fresh autologous embryos are affected by age and also other factors. These factors vary among women, such as body mass index, smoking, ethnicity, number of embryos transferred, cause and duration of infertility, previous pregnancy (Cai et al., 2011; CDC, 2012b, 2013b, 2014b, 2015b, 2016b; Choi et al., 2013; Hunault et al., 2002; Nelson and Lawlor, 2011; Ottosen et al., 2007; Templeton et al., 1996; Vaegter et al., 2017; van Loendersloot et al., 2010, 2013, 2014) but also among, and even within, assisted reproduction technique clinics, which were not taken into account in our study, hence a limitation of our study. As age is the most important factor determining success rates in those cycles, however, our study describes the 'observed pattern,' at the population level, by which success rates change with 'the most important factor' (age) rather than with factors less important than age. Templeton et al. (1996) analysed live births in 36,961 IVF cycles registered with the HFEA in the UK between August 1991 (start of register) and April 1994, and suggested that a few factors other than age should also be taken into account when predicting success rates, 'unless future studies are very large or correctly randomised.' Therefore, the fact that we used a very large number (488,351) of assisted reproduction technique cycles (from the population), and took into account the most important factor (age), should alleviate this limitation. Nelson and Lawlor (2011) also analysed live births on HFEA data between 2003 and 2007 in 144,018 IVF cycles, and reported that odds ratios for live births within age groups were similar when they were calculated taking only age into account (univariable) versus other factors along with age (multivariable). Therefore, age alone can be used to develop models for success rates when using a very large number of cycles, e.g., in the population, as in this study.

As the data in this study were from a very large number (488,351) of assisted reproduction technique cycles in the 'accessible population,' we were able to detect highly significant ($P \leq 0.02$) differences, in outcomes between two consecutive ages, as small as one percentage point, e.g., a 0.97 percentage-point difference in live birth per started cycle between the ages of 29 and 30 years; 42.35% versus 41.38%; $P = 0.02$ (**Figure 1A**); a 1.1 percentage-point difference in pregnancy per started cycle between age 31 and 32; 46.58% versus 45.48%; $P = 0.004$ (**Figure 1B**); and a 1.25 percentage-point difference in live birth per pregnancy between the ages of 31 and 32 years; 87.79% versus 86.54%; $P = 0.01$ (**Figure 1C**). Although these small (but statistically highly significant) differences in the population may not seem clinically meaningful, they are likely to manifest themselves with much greater, and hence with clinically more meaningful, differences in smaller samples, at individual assisted reproduction technique clinics, or both. For example, the numbers of cycles carried out by individual US assisted reproduction technique clinics in 2014 ranged from as few as two to 7648 (CDC, 2016a).

It is assumed that success rates in assisted reproduction technique cycles initially remain stable with age, and decline steadily after 30s or mid-30s (CDC, 2012b, 2013b, 2014b, 2015b, 2016b, p18 or 20; HFEA, 2016). In our study, however, assisted reproduction technique success rates at the population level are not initially stable with age but, by following well-fitted, ∩-shaped curvilinear regressions with age, they initially and steadily increase to age 28 years, and decline steadily thereafter. Accordingly, and also in contrast to the aforementioned assumption, our study also shows that the effect of increasing age on success rates can be either positive or negative, depending on age: positive effect to the age of 28 years, and negative effect after the age of 28 years. That increasing age to 28 years exerts a positive effect on success rates also means that, in women aged less than 29 years, the younger the woman the lower the success rates, i.e., adverse effect of younger age on success rates among women aged less than 29 years, similar to the adverse effect of older age among women aged 29 years and older, albeit to a lesser, but still significant, extent. For this reason, among women aged less than 29 years, success rates were lower in women aged less than 25 years than in women aged between 25 and 28 years; and women who had unsuccessful outcomes were younger than those who had successful outcomes. Conversely, within subsequent age groups (≥29 years), women who had unsuccessful outcomes were older than those who had successful outcomes.

Although the adverse effect of older age after mid-30s on success rates (declining portion of the ∩-shaped curvilinear regression) is well established (Cai et al., 2011; CDC, 2012b, 2013b, 2014b, 2015b, 2016b; Choi et al., 2013; Hunault et al., 2002; Nelson and Lawlor, 2011; Ottosen et al., 2007; Templeton et al., 1996; Vaegter et al., 2017; van Loendersloot et al., 2010, 2013, 2014), the adverse effect of younger age among women aged less than 29 years on success rates (initial, increasing portion of the ∩-shaped curvilinear regression) has received little attention. This is most likely because of the adverse effect of younger age among women aged less than 29 years being to a lesser extent (albeit still significant) compared with the adverse effect of older age among women aged 29 years and older. Our finding of adverse effect of younger age among women aged less than 29 years on success rates agrees with a previous report (Wu et al., 2012) that, in IVF cycles using fresh autologous embryos, live birth and clinical pregnancy rates were significantly lower in women younger than 25 years than in women age 25–29 years and 30–34 years. Ottosen et al. (2007) also reported odds ratios for pregnancy (with elective single embryo transfers) initially increasing within age groups, and declining thereafter, with odds ratios of 0.67, 1.00, 0.78, 0.53, and 0.32 in women aged 19–24, 25–29, 30–34, 35–39, and ≥40 years, respectively. This would suggest an adverse effect of age before the age of 25 years as well as an overall ∩-shaped curvilinear relationship. The adverse effect of younger age among women aged less than 29 years on live births was also reported by Templeton et al. (1996), who analysed data in 36,961 IVF cycles registered with the HFEA in the UK between 1991 and 1994. Similar to the findings of the present study, they reported that live birth rate per cycle at every age before the age of 25 years was lower than the highest rates between the ages of 25 and 30 years. Although they also proposed a ∩-shaped curvilinear regression model between live birth per cycle and age, their model did not fit well for women aged under 25 years, which they ascribed to very small numbers of cycles and live births for those ages. To the best of our knowledge, the present study is the first to report ∩-shaped curvilinear regression models between age and success rates that are not only extremely well-fitting and highly significant but also at the population level.

This study also shows that miscarriage rates, conversely by following well-fitted, ∪-shaped curvilinear regressions with age, initially and steadily decline to the age of 28 years, and increase steadily thereafter. Accordingly, very young ages (as with older ages) are associated with lower pregnancy per started cycle and also, in those who get pregnant, with higher miscarriage per pregnancy, both of which, in turn, contribute to lower live birth per started cycle in those very young women. In other words, even if very young women can get pregnant, miscarriage is higher in those young pregnant women (as with older pregnant women, albeit to a lesser, but still significant, extent). Whether very young age in egg donors is also associated with higher miscarriage rate, lower assisted reproduction technique success rates, or both, warrants further study.

Although the adverse effect of advancing age (after mid-30s) on natural fertility, hence on assisted reproduction technique success rates, is mainly due to declining egg quality (degenerative or ageing eggs), quantity with age, or both (Frank et al., 1994; Gindoff and Jewelewicz, 1986; Jansen, 1984; Lim and Tsakok, 1997; Navot et al., 1991; O'Connor et al., 1998; Speroff, 1994), how very young age among

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women aged less than 29 years exerts its adverse effect (albeit to a lesser extent) on assisted reproduction technique success rates is unclear. It is possible that, although older women may be seeking infertility treatment mostly for age/egg related problems, some very young women may suffer from severe non-age/egg related problems, unexplained infertility or premature ovarian failure, which may decrease the efficiency of assisted reproduction technique treatment in those very young women. Recent studies have also shown that blastocyst aneuploidy rate is higher in very young women than in those in their mid–30s, although not as high as in older women (Eva M et al., 2016; Franasiak et al., 2014; McCoy et al., 2015), which may also be the reason for lower assisted reproduction technique success rates in very young women. Those studies have reported that blastocyst aneuploidy rate changes with age following ∪–shaped curvilinear regressions, initially and steadily declining before the age of 30 years, and increasing steadily thereafter. These ∪–shaped curvilinear regressions reported between aneuploidy rate and age are similar to the ∪–shaped curvilinear regression in our study between miscarriage rate and age, and the reverse (flipped) version of the ∩–shaped curvilinear regression in our study between success rates and age. Therefore, it is possible that the higher incidence of embryo aneuploidy in very young women may prevent embryo implantation or cause miscarriage, by which very young age may exert its adverse effect on assisted reproduction technique success rates.

Although it is widely assumed that success rates decline steadily after the ages of 30–35 years (CDC, 2012b, 2013b, 2014b, 2015b, 2016b; HFEA, 2016), our study shows that the steady decline in success rates begins earlier, after the age of 28 years. In agreement with our finding, Vaegter et al. (2017) reported that the first marked decline in live birth rate with age occurred after the age of 28 years (where only single embryos were transferred). Templeton et al. (1996) also reported that the steady decline in live birth rates began after the highest live birth rates in women aged between 25 and 30 years.

Although the effects of younger ages among women aged less than 29 years and of older ages among women aged between 29 and 34 were both negative on each success rate (with positive and negative slopes within age groups, respectively), they did not cancel one another out but resulted in lower success rates in women aged between 29 and 34 years than in women aged less than 29 years. This was because the negative effect of older ages among women aged between 29 and 34 years was to a greater extent compared with the negative effect of younger ages among women aged less than 29 years. Accordingly, for each assisted reproduction technique outcome, the magnitude of the negative slope in women aged between 29 and 34 years was greater than the magnitude of the positive slope in women aged less than 29 years (e.g., 2.4 times for live birth per started cycle, or −1.36 versus 0.56; and 3.4 times for pregnancy per cycle, or −1.19 versus 0.35).

Our findings indicate that the decline in success rates (after the age of 28 years) occurs more rapidly at every age than that at the preceding age, i.e., at increasing rates. This may suggest that the major underlying causes of declining assisted reproduction technique success rates after the age of 28 years (such as, declining egg quality and quantity, or degenerative or ageing eggs) may also occur at increasing rates at every age. To the best of our knowledge, our study is the first to show that the age–driven decline in assisted reproduction technique success rates occurs at increasing rates.

In conclusion, although it has been known that assisted reproduction technique success rates in cycles using fresh autologous embryos decline with advancing age, our study shows that, for the first time, and in the population, success rates change with age following well–fitted, ∩–shaped curvilinear regressions; miscarriage follows similar but reverse ∪–shaped curvilinear regressions, as a result of which success rates increase steadily to the age of 28 years, and decline steadily thereafter, whereas miscarriage rate declines steadily to the age of 28 years, and increases steadily thereafter. In other words, very young ages (as with older ages, albeit to a lesser, but still significant, extent) are associated with lower live–birth and pregnancy rates and also, in those women who become pregnant, with higher miscarriage rate. Our study also shows that, for the first time, and in the population, the initial age–driven increase in success rates occurs at decreasing rates and the subsequent decline occurs at increasing rates; and conversely, the initial age–driven decline in miscarriage rate occurs at decreasing rates, and the subsequent increase occurs at increasing rates. That the age–driven decline in success rates begins as early as before the age of 30 years and also occurs at increasing rates suggests that women who are older than 30 years of age with infertility problems should not delay assisted reproduction technique treatment, if assisted reproduction techniques are their only option. Whether very young age of egg donors is also associated with lower success rates, higher miscarriage rate, or both, warrants further study. The pattern of change in success rates with age in assisted reproduction technique cycles using frozen autologous embryos also warrants further study.

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Appendix: Supplementary material

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