

<b>HEADINGS</b>	<b>DESCRIPTION</b>
<b>Bibliographic citation</b>	Nelson SM, Lawlor DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144,018 treatment cycles. PLoS Med. 2011 Jan 4;8(1):e1000386. <a href="http://www.ncbi.nlm.nih.gov/pubmed/21245905">http://www.ncbi.nlm.nih.gov/pubmed/21245905</a>
<b>Sources of funding</b>	UK Medical Research Council (G0600705) and the University of Bristol
<b>Competing interest</b>	The authors have declared that no competing interests exist
<b>Setting</b>	National database licensed fertility treatment, United Kingdom
<b>Objective(s) of the study</b>	To assess the extent to which baseline characteristics can be used to predict live birth after IVF-assisted conception, and for those cycles in which a singleton pregnancy was achieved to identify which factors were associated with preterm delivery, low birth weight, and macrosomia.
<b>Type of prognostic study</b>	Outcome prediction study
<b>METHODS</b>	
<b>Study design (cited by author or actual)</b>	Prospective cohort study
<b>Sampling method</b>	Not reported
<b>Eligibility criteria</b>	Treatment cycles that were for storage or donation of gametes, were not IVF, or were frozen embryo transfers were excluded.
<b>Follow-up moments</b>	All treatment cycles in January 2003 – December 2007
<b>Outcome measures</b>	Main outcome: At least one live birth ( which was defined as any birth event in which at least one baby was born alive and survived for more than 1 mo).  Other outcomes: adverse perinatal outcomes (preterm, extreme preterm, low birth weight, and macrosomia)
<b>Prognostic factors and potential</b>	<i>In case of a prognostic factor study:</i>

**confounders**

*In case of an outcome prediction study:*

**Table 1.** Associations of potential predictors for live birth following IVF.

Characteristic	Categories	Univariable Odds Ratio of Live Birth (95% CI)	Multivariable <sup>a</sup> Odds Ratio of Live Birth (95% CI)	p-Value <sup>b</sup>
Maternal age (years)	18–34	1	1	<0.001
	35–37	0.77 (0.75–0.79)	0.78 (0.76–0.81)	
	38–39	0.53 (0.51–0.55)	0.53 (0.51–0.56)	
	40–42	0.29 (0.28–0.30)	0.29 (0.28–0.31)	
	43–44	0.10 (0.09–0.12)	0.10 (0.09–0.12)	
	45–50	0.15 (0.12–0.19)	0.12 (0.09–0.15)	
Duration of infertility (years)	<1	1.48 (1.34–1.65)	1.51 (1.35–1.68)	<0.001
	1–3	1.10 (1.07–1.13)	1.11 (1.08–1.15)	
	4–6	1	1	
	7–9	0.91 (0.87–0.94)	0.94 (0.91–0.98)	
	9–12	0.81 (0.76–0.85)	0.87 (0.82–0.92)	
	>12	0.71 (0.67–0.75)	0.89 (0.84–0.95)	
Cause of infertility	Unknown	1	1	<0.001
	Tubal only	0.94 (0.90–0.97)	0.87 (0.83–0.90)	
	Anovulatory only	0.93 (0.88–0.98)	0.95 (0.90–1.00)	
	Endometriosis only	1.05 (0.98–1.13)	0.96 (0.89–1.03)	
	Cervical only	0.41 (0.20–0.85)	0.39 (0.19–0.82)	
	Male only	1.16 (1.13–1.20)	0.91 (0.87–0.95)	
	Combination known causes	1.01 (0.96–1.06)	0.88 (0.83–0.92)	
Number of previous unsuccessful IVF	0	1	1	<0.001
	1	0.74 (0.70–0.79)	0.72 (0.65–0.81)	
	2	0.69 (0.64–0.76)	0.70 (0.62–0.80)	
	3	0.74 (0.66–0.84)	0.77 (0.66–0.91)	
	4	0.51 (0.42–0.62)	0.55 (0.45–0.69)	
	≥5	0.57 (0.48–0.69)	0.68 (0.55–0.83)	
Mutually exclusive categories of previous IVF and obstetric history	No previous IVF, 0 pregnancy	1	1	<0.001
	No previous IVF, at least 1 pregnancy, 0 live births	0.88 (0.86–0.91)	1.03 (0.99–1.06)	
	No previous IVF, at least 1 pregnancy, at least 1 live birth	0.92 (0.88–0.96)	1.19 (1.14–1.24)	
	Previous IVF, 0 pregnancy	0.72 (0.68–0.76)	1.14 (1.01–1.28)	
	Previous IVF, at least 1 pregnancy, 0 live birth	0.68 (0.64–0.73)	1.02 (0.93–1.11)	
	Previous IVF, at least 1 pregnancy, at least 1 live birth	1.10 (1.03–1.17)	1.58 (1.46–1.71)	
Hormonal preparation	Antioestrogen	1	1	<0.001
	Gonadotrophin	1.43 (1.24–1.63)	1.33 (1.15–1.53)	
	Hormone replacement	1.61 (1.38–1.89)	1.55 (1.31–1.82)	
Cycle number	1	1	1	<0.001
	2	0.80 (0.78–0.83)	0.85 (0.82–0.87)	
	≥3	0.76 (0.74–0.79)	0.88 (0.85–0.91)	
Source of egg	Donor	1	1	<0.001
	Patient	0.87 (0.74–1.02)	0.38 (0.32–0.45)	
Treatment type	IVF	1	1	<0.001
	ICSI plus IVF	1.28 (1.25–1.31)	1.27 (1.23–1.31)	

N = 144,018 analysis cohort with complete data on all variables included in any model.

<sup>a</sup>Multivariable adjusted = mutual adjustment for all variables listed in column one.

<sup>b</sup>p-Value for multivariable association; all p-values are likelihood ratio tests of null hypothesis that the odds are the same for each category (i.e., they do not assume linearity).

**RESULTS**

**Numbers**

Eligible N=163,425. Missing: N=19,407. Analysed: N=144,018.

**Patients characteristics**

See table 1 above

**Outcome measures data**

Rate of live births: 23.4% (95% CI: 23.2–23.7)  
 Rate of macrosomia: 9.3%  
 Rate of Low Birth Weight: 8.7%  
 Rate of extreme preterm (<33 wk gestation): 2.0%  
 Rate of preterm (≤36 wk gestation): 8.6%

**Effect size of prognostic factors**  
(in case of a prognostic factor study, or an outcome prediction study.)

*In case of a prognostic factor study:*

*In case of an outcome prediction study:*

*See table 1 above and as regards interaction effects:*

**Associations of duration of infertility and source of oocyte with live birth, stratified by maternal age**

Characteristic	Categories of characteristics	Odds ratio (95%CI) of association with live birth by categories of maternal age (Years):				
		18-34	35-37	38-39	40-42	>=43
Duration of infertility (years)	<1	1.50 (1.29, 1.74)	1.49 (1.92, 1.86)	1.64 (1.23, 2.19)	1.70 (1.21, 2.40)	-*
	1-3	1.14 (1.10, 1.19)	1.10 (1.03, 1.16)	1.05 (0.96, 1.14)	1.07 (0.95, 1.20)	1.02 (0.73, 1.42)
	4-6	1	1	1	1	1
	7-9	0.92 (0.87, 0.97)	0.97 (0.90, 1.05)	0.96 (0.86, 1.07)	0.96 (0.82, 1.12)	1.10 (0.74, 1.65)
	9-12	0.86 (0.79, 0.93)	0.86 (0.79, 0.96)	0.91 (0.78, 1.05)	0.92 (0.75, 1.13)	0.55 (0.29, 1.07)
	>12	0.86 (0.78, 0.96)	0.89 (0.78, 0.96)	0.97 (0.86, 1.11)	0.86 (0.72, 1.03)	0.60 (0.37, 0.96)
Source of egg	Donor	1	1	1	1	1
	Patient	1.04 (0.69, 1.54)	0.63 (0.40, 0.99)	0.71 (0.43, 1.14)	0.29 (0.20, 0.42)	0.11 (0.79, 1.44)

**Associations of causes of infertility and number of treatment cycles with live birth, stratified by use of ICSI.**

Characteristic	Categories of characteristic	Odds ratio (95%CI) of association with live birth by categories of whether ICSI used or not:	
		ICSI	No ICSI
Main cause of infertility	Unknown	1	1
	Tubal	0.80 (0.72, 0.88)	0.86 (0.83, 0.91)
	Anovulatory	1.02 (0.92, 1.13)	0.92 (0.87, 0.98)
	Endometriosis	0.95 (0.81, 1.11)	0.96 (0.88, 1.04)
	Cervical	1.30 (0.23, 7.40)	0.32 (0.14, 0.73)
	Male	1.02 (0.97, 1.08)	0.76 (0.72, 0.81)
	Combination	0.99 (0.93, 1.07)	0.80 (0.61, 0.83)
Number of treatment cycles	1	1	1
	2	0.84 (0.81, 0.88)	0.85 (0.81, 0.89)
	>=3	0.82 (0.78, 0.86)	0.97 (0.92, 1.01)

Risk factors for preterm, low birth weight, and macrosomia:

**Univariable associations of potential risk factors with preterm birth, low birth weight and macrosomia amongst singleton births following IVF.**

Characteristic	Categories	Univariable association with preterm birth. N = 24096 in analyses with n = 2070 cases of preterm birth		Univariable association with low birth weight. N = 21804 in analyses with n = 2100 cases of low birth weight		Univariable association with low birth weight. N = 21950 in analyses with n = 2246 case of macrosomia	
		Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Age (years)	18-34	1	0.25	1	0.04	1	< 0.001
	35-37	0.92 (0.82, 1.01)		0.88 (0.79, 0.98)		1.18 (1.06, 1.30)	
	38-39	0.90 (0.78, 1.04)		0.86 (0.75, 0.99)		1.13 (1.00, 1.30)	
	>=40	1.01 (0.86, 1.21)		1.01 (0.85, 1.19)		1.33 (1.13, 1.56)	
Duration of infertility (years)	<1	1.14 (0.81, 1.62)	0.002	0.90 (0.62, 1.30)	0.04	0.87 (0.61, 1.24)	0.05
	1-3	0.99 (0.88, 1.10)		0.93 (0.84, 1.03)		0.90 (0.81, 0.99)	
	4-6	1		1			
	7-9	1.17 (1.01, 1.34)		1.06 (0.92, 1.22)		1.06 (0.93, 1.21)	
	>=9	1.29 (1.12, 1.49)		1.16 (1.00, 1.34)		1.05 (0.90, 1.21)	
Cause	Unknown	1	< 0.001	1	0.001	1	0.009
	Tubal only	1.27 (1.11, 1.47)		1.15 (1.00, 1.33)		1.08 (0.94, 1.25)	
	Anovulatory only	1.21 (1.01, 1.44)		1.26 (1.06, 1.51)		1.03 (0.86, 1.24)	
	Endometriosis only	0.86 (0.65, 1.14)		1.05 (0.82, 1.37)		0.92 (0.71, 1.20)	
	Cervical only	8.18 (1.83, 36.65)		14.67 (2.45, 87.98)		8.28 (1.30, 66.01)	
	Male only	0.89 (0.79, 1.00)		0.96 (0.85, 1.08)		1.14 (1.02, 1.28)	
	Combination known causes	1.17 (1.00, 1.38)		1.13 (0.96, 1.34)		0.89 (0.75, 1.06)	
Previous unsuccessful IVF (number)	0	1	0.90	1	0.25	1	0.64
	1	1.05 (0.84, 1.30)		1.21 (0.98, 1.49)		0.87 (0.69, 1.09)	
	2	1.10 (0.80, 1.53)		1.17 (0.85, 1.61)		0.93 (0.66, 1.30)	
	>=3	0.94 (0.65, 1.36)		0.93 (0.65, 1.34)		1.02 (0.72, 1.42)	

	Mutually exclusive categories of previous IVF and obstetric history	No previous IVF, 0 pregnancy	1	0.006	1	< 0.001	1	0.001	
		No previous IVF, at least 1 pregnancy, 0 live births	1.25 (1.12, 1.41)		1.18 (1.04, 1.32)		1.20 (1.07, 1.34)		
		No previous IVF, at least 1 pregnancy, at least 1 live birth	1.07 (0.92, 1.25)		0.86 (0.73, 1.03)		1.28 (1.11, 1.48)		
		Previous IVF, 0 pregnancy	1.14 (0.94, 1.40)		1.23 (1.01, 1.49)		0.95 (0.77, 1.17)		
		Previous IVF, at least 1 pregnancy, 0 live birth	1.18 (0.93, 1.52)		1.22 (0.96, 1.55)		0.97 (0.75, 1.26)		
		Previous IVF, at least 1 pregnancy, at least 1 live birth	0.98 (0.76, 1.25)		0.82 (0.63, 1.07)		1.31 (1.06, 1.62)		
	Hormonal preparation	Antioestrogen	1	0.11	1	0.94	1	0.88	
		Gonadatropin	0.68 (0.44, 1.05)		0.92 (0.56, 1.50)		1.04 (0.63, 1.72)		
		Hormone replacement	0.81 (0.49, 1.35)		0.93 (0.53, 1.63)		1.11 (0.63, 1.96)		
	Cycle number	1	1	0.64	1	0.38	1	0.002	
		2	1.00 (0.90, 1.13)		0.97 (0.87, 1.09)		1.09 (0.98, 1.22)		
		>=3	0.95 (0.84, 1.07)		0.92 (0.81, 1.04)		1.22 (1.09, 1.36)		
	Source of egg	Donor	1	< 0.001	1	< 0.001	1	0.09	
		Patient	0.38 (0.25, 0.57)		0.40 (0.26, 0.63)		0.64 (0.38, 1.07)		
	Treatment type	IVF	1	0.02	1	0.004	1	0.58	
		IVF & ICSI	0.83 (0.76, 0.91)		0.88 (0.80, 0.96)		1.02 (0.94, 1.12)		
	<p>Cycles include in analyses are those with complete data on all variables and who experienced a singleton birth after IVF. For associations with low birth weight, those with macrosomia as outcome are removed so that low birth weight is compared with normal birth weight and similarly for macrosomia those with low birth weight are removed so that macrosomia is compared with normal birth weight. P-values are likelihood ratio tests of null hypothesis that the odds are the same for each category (i.e. they do not assume linearity)</p>								

**Table 5.** Multivariable associations of potential risk factors with preterm birth, low birth weight and macrosomia amongst singleton births following IVF.

Characteristic	Categories	Multivariable Association with Preterm Birth; N=24,096 in Analyses with n=2,070 Cases of Preterm Birth		Multivariable Association with Low Birth Weight; N=21,804 in Analyses with n=2,100 Cases of Low Birth Weight		Multivariable Association with Low Birth Weight; N=21,950 in Analyses with n=2,246 Cases of Macrosomia	
		Odds Ratio (95%CI)	p-Value	Odds Ratio (95%CI)	p-Value	Odds Ratio (95%CI)	p-Value
Age, y	18-34	1	0.12	1	0.04	1	0.01
	35-37	0.90 (0.80-1.00)		0.87 (0.78-0.97)		1.14 (1.03-1.27)	
	38-39	0.87 (0.75-1.00)		0.86 (0.74-0.99)		1.09 (0.95-1.25)	
	≥40	0.93 (0.77-1.10)		0.96 (0.80-1.15)		1.25 (1.06-1.48)	
Duration of infertility, y	<1	1.05 (0.73-1.49)	0.004	0.86 (0.58-1.25)	0.01	0.81 (0.56-1.17)	0.20
	1-3	0.96 (0.86-1.07)		0.90 (0.80-1.00)		0.90 (0.81-0.99)	
	4-6	1		1		1	
	7-9	1.17 (1.02-1.35)		1.07 (0.93-1.24)		1.02 (0.89-1.16)	
	≥9	1.25 (1.07-1.46)		1.16 (1.00-1.36)		0.93 (0.80-1.09)	
Cause	Unknown	1	<0.001	1	0.02	1	0.002
	Tubal only	1.22 (1.06-1.41)		1.12 (0.97-1.30)		1.06 (0.91-1.22)	
	Anovulatory only	1.14 (0.95-1.37)		1.19 (1.00-1.42)		1.04 (0.86-1.25)	
	Endometriosis only	0.86 (0.65-1.14)		1.04 (0.80-1.35)		0.96 (0.73-1.25)	
	Cervical only	9.09 (2.01-41.13)		15.62 (2.59-94.06)		10.46 (1.46-74.85)	
	Male only	0.95 (0.83-1.09)		1.02 (0.89-1.17)		1.22 (1.07-1.39)	
	Combination known causes	1.19 (1.00-1.41)		1.15 (0.97-1.36)		0.92 (0.77-1.11)	
Previous unsuccessful IVF, number	0	1	0.44	1	0.37	1	0.95
	1	0.75 (0.50-1.15)		0.85 (0.56-1.29)		0.92 (0.77-1.10)	
	2	0.80 (0.50-1.30)		0.82 (0.51-1.32)		0.92 (0.61-1.38)	
	≥3	0.66 (0.40-1.11)		0.63 (0.38-1.06)		0.98 (0.61-1.58)	
Mutually exclusive categories of previous IVF and obstetric history	No previous IVF, 0 pregnancy	1	0.11	1	0.004	1	<0.001
	No previous IVF, at least 1 pregnancy, 0 live births	1.15 (0.40-1.11)		1.13 (1.00-1.27)		1.23 (1.09-1.39)	
	No previous IVF, at least 1 pregnancy, at least 1 live birth	0.99 (0.84-1.16)		0.83 (0.70-0.98)		1.28 (1.11-1.49)	
	Previous IVF, 0 pregnancy	1.48 (0.95-2.30)		1.54 (1.00-2.39)		0.97 (0.63-1.49)	
	Previous IVF, at least 1 pregnancy, 0 live birth	1.30 (0.93-1.80)		1.37 (0.99-1.91)		1.02 (0.72-1.43)	
	Previous IVF, at least 1 pregnancy, at least 1 live birth	1.02 (0.55-1.38)		0.89 (0.67-1.17)		1.30 (1.03-1.63)	
Hormonal preparation	Antioestrogen	1	0.11	1	0.77	1	0.86
	Gonadotrophin	0.87 (0.55-1.39)		1.18 (0.71-1.97)		1.08 (0.64-1.83)	
	Hormone replacement	1.07 (0.63-1.82)		1.24 (0.69-2.21)		1.15 (0.64-2.07)	
Cycle number	1	1	0.43	1	0.17	1	0.04
	2	1.00 (0.89-1.13)		0.96 (0.85-1.08)		1.07 (0.96-1.20)	
	≥3	0.92 (0.81-1.05)		0.89 (0.78-1.01)		1.17 (1.04-1.31)	
Source of egg	Donor	1	<0.001	1	<0.001	1	0.16
	Patient	0.41 (0.26-0.64)		0.42 (0.26-0.68)		0.68 (0.39-1.17)	
Treatment type	IVF	1	0.05	1	0.05	1	0.46

**Table 2.** AUROC for the Templeton and novel method of predicting live birth with IVF.

Model	AUROC (95% Confidence Interval)	p-Value Comparing Models
Templeton	0.6184 (0.6152-0.6217)	ref
Novel model	0.6335 (0.6202-0.6367)	<0.001

N=144,018 analysis cohort with complete data on all variables included in any model. Templeton: As in reference [7], to date the only externally validated prediction model. Novel model: using the same variables as Templeton but allowing them to have different multivariable coefficients to those originally derived by Templeton and including terms for all causes of infertility (rather than just tubal versus other, as in the original Templeton) and four additional predictors: type of hormonal preparation, whether egg came from patient or donor, number of treatment cycles, and whether ICSI was used with the IVF.  
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**Table 3.** Calibration of the two prediction models.

Tenth of the Distribution of the Linear Predictor	Templeton Prediction Model <sup>a</sup>			Novel Prediction Model <sup>b</sup>		
	Observed Live Birth Rate per 100 Cycles of Treatment (95% CI)	Predicted Live Birth Rate per 100 Cycles of Treatment (95% CI)	Ratio Predicted to Observed	Observed Live Birth Rate per 100 Cycles of Treatment (95%CI)	Predicted Live Birth Rate per 100 Cycles of Treatment (95%CI)	Ratio Predicted to Observed
Lowest 10 <sup>th</sup>	8.36 (7.91–8.81)	3.57 (3.54–3.59)	0.43	7.66 (7.23–8.09)	7.23 (7.18–7.28)	0.94
2 <sup>nd</sup>	13.66 (13.10–14.22)	6.44 (6.43–6.45)	0.47	13.21 (12.66–13.76)	13.16 (13.13–13.18)	1.00
3 <sup>rd</sup>	18.67 (18.04–19.29)	8.45 (8.43–8.46)	0.45	18.15 (17.53–18.78)	18.00 (17.99–18.02)	1.00
4 <sup>th</sup>	22.77 (22.14–23.40)	10.26 (10.25–10.26)	0.45	20.42 (19.76–21.08)	21.10 (21.09–21.11)	1.03
5 <sup>th</sup>	23.30 (22.51–24.07)	11.61 (11.60–11.62)	0.50	23.40 (22.71–24.08)	23.63 (23.62–23.63)	1.01
6 <sup>th</sup>	25.41 (24.77–26.05)	13.31 (13.30–13.32)	0.52	24.87 (24.18–25.56)	25.57 (25.57–25.59)	1.03
7 <sup>th</sup>	29.93 (29.22–30.64)	13.69 (13.69–13.69)	0.46	27.04 (26.30–27.77)	27.43 (27.42–27.44)	1.01
8 <sup>th</sup>	26.78 (25.87–27.67)	14.77 (14.76–14.78)	0.55	30.37 (29.62–31.12)	29.35 (29.34–29.36)	0.97
9 <sup>th</sup>	31.85 (31.21–32.50)	17.29 (17.28–17.30)	0.54	32.26 (31.54–32.98)	31.95 (31.94–31.97)	0.99
Highest 10 <sup>th</sup>	33.26 (32.23–34.22)	20.91 (20.84–20.98)	0.63	36.50 (35.66–37.34)	36.47 (36.43–35.61)	1.00

N= 144,018 analysis cohort with complete data on all variables included in any model. The cohort is split into 10ths of the distribution of the linear predictor for each of the two prediction models. For example, for the Templeton prediction model the observed and predicted are compared by 10<sup>th</sup> of the Templeton linear predictor.  
<sup>a</sup>Templeton: As in reference [7], to date the only externally validated prediction model (Text S1).  
<sup>b</sup>Novel model: Using the same variables as Templeton but allowing them to have different multivariable coefficients to those originally derived by Templeton and including terms for all causes of infertility (rather than just tubal versus other as in the original Templeton) and four additional predictors: type of hormonal preparation, whether egg came from patient or donor, number of treatment cycles, and whether ICSI was used with the IVF (Text S2).  
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**Authors conclusion** Our results show that couple- and treatment-specific factors can be used to provide infertile couples with an accurate assessment of whether they have low or high risk of a successful outcome following IVF.

**CRITICAL APPRAISAL OF THE STUDY QUALITY**

<b>Validity of results</b>	
<b>Addendum Optional</b>	