International Journal of Technology Assessment in Health Care, 31:6 (2015), 426–433.

doi:10.1017/S0266462315000628

DEFINING ELIGIBILITY CRITERIA FOR FUNDING POLICIES AROUND *IN VITRO* FERTILIZATION

Devidas Menon
Health Technology and Policy Unit, School of Public Health, Department of Public Health Sciences, University of Alberta, Research Transition Facility
menon@ualberta.ca

Alexa A. Nardelli
Health Technology and Policy Unit, School of Public Health, Department of Public Health Sciences, University of Alberta, Research Transition Facility

Tarek Motan
Division of Reproductive Endocrinology & Infertility, Department of Obstetrics & Gynaecology

Kristin Klein
Faculty of Medicine and Dentistry, University of Alberta, Research Transition Facility

Tania Stafinski
Health Technology and Policy Unit, School of Public Health, Department of Public Health Sciences, University of Alberta, Research Transition Facility

Objectives: This review aims to assess the state of the science around the potential impact of certain patient characteristics on the safety and effectiveness of *in vitro* fertilization (IVF).
Methods: Following Cochrane Collaboration guidelines and the PRISMA statement, a comprehensive systematic review of reviews and recent primary studies examining the impact of paternal age and maternal age, smoking, and body mass index (BMI) on the safety and effectiveness of IVF was performed. Papers, published between January 2007 and June 2014, were independently reviewed and critically appraised by two researchers using published quality assessment tools for reviews and primary studies. Due to heterogeneity across papers (different study designs and patient selection criteria), a qualitative analysis of extracted information was performed.
Results: Seventeen papers (ten systematic reviews and seven primary studies) were included. They comprised evidence from retrospective observational studies in which maternal age, BMI, and smoking status were explored as part of secondary analyses of larger studies. The majority of papers found that the likelihood of achieving a pregnancy was lower among women who were >40 years, had a BMI ≥ 25 and smoked. Advanced maternal age and BMI were also associated with higher rates of preterm birth and low birth weight.
Conclusions: Based on available evidence, it may be appropriate to consider "maternal age" and "morbid obesity" in public funding policies that aim to maximize the effectiveness of IVF. However, given inconsistencies in the effect of smoking across different pregnancy-related outcomes, support for incorporating it into funding conditions appears weak.

Keywords: *In vitro* fertilization, Eligibility criteria, Safety, Effectiveness

The Alberta Health Technologies Decision Process (AHTDP) was established a decade ago to inform decisions on the public funding of nondrug health technologies by the provincial government. Since then, approximately fifty health technology assessments (HTAs) have been initiated, including one on *in vitro* fertilization (IVF).

In Alberta, IVF is not publicly funded. However, the ministry of health was recently asked to reconsider this position. As a result, an HTA of IVF was conducted under the auspices of the AHTDP. While the HTA was to address standard questions related to the safety, effectiveness and economic implications of IVF, its scope also included what is known about the effect of certain patient characteristics on clinical outcomes. Such information was needed to inform discussions around whether it may be clinically appropriate to consider incorporating patient eligibility criteria into funding decisions. This study reports on the systematic review undertaken to determine the state of the science around the potential impact of certain patient characteristics on the safety and effectiveness of IVF.

The authors thank Leigh-Ann Topfer for conducting the literature searches. This work was part of a health technology assessment on assisted reproductive technologies in Alberta conducted by the Health Technology and Policy Unit for Alberta Health. Production of this work has been made possible by a financial contribution from Alberta Health and under the auspices of the Alberta Health Technologies Decision Process: the Alberta model for health technology assessment and policy analysis. The views expressed herein do not necessarily represent the official policy of Alberta Health.

BACKGROUND

Infertility is clinically defined as the failure to achieve a clinical pregnancy following at least 12 months of unprotected sexual intercourse (1–3) (see Table 1 for descriptions of key terms in this study). Similar to prevalence rates reported in other western countries, approximately 10 to 15 percent of couples in Canada experience clinical infertility (4;5).

It is well recognized that IVF is an effective treatment option for many couples with infertility. Demand for the procedure has grown, along with its use in broader patient populations, including postmenopausal women (6). However, neither its safety with respect to the procedure, pregnancy, and delivery in these broader populations, nor its effect on any offspring have been fully determined (7–10). Therefore, in an effort to balance

Table 1. Key Terms and Definitions

Procedure	Description
Assisted reproductive technologies (ARTs)	Any procedures that involve the in vitro manipulation of oocytes and sperm, or embryos, to establish pregnancy
Controlled ovarian stimulation (COS)	The use of fertility drugs to stimulate the ovaries to produce multiple eggs; also called ovulation induction
Ectopic pregnancy	When the fertilized egg implants outside of the uterus, usually in the fallopian tube
Embryo	A fertilized egg during the first 8 weeks (56 days) after fertilization, after which it is called a fetus
Gestational diabetes	High blood sugar diagnosed during pregnancy
Gestational hypertension	High blood pressure during pregnancy
In vitro fertilization (IVF)	An ARTs procedure where the egg is fertilized by the sperm outside of the woman's body; the steps involved in IVF include: ovarian stimulation, egg retrieval, egg fertilization, embryo culture and embryo transfer
Infertility	Failure to achieve a clinical pregnancy following at least 12 months of unprotected sexual intercourse
Intracytoplasmic sperm injection (ICSI)	A procedure performed in conjunction with IVF whereby a single sperm is injected into a mature egg
Low birth weight (LBW)	Birth weight of <2,500 grams (about 5.5 lbs); very low birth weight = birth weight <1,500 grams; extremely low birth weight = birth weight <1,000 grams
Miscarriage	Loss of pregnancy before 20 weeks gestation
Oocyte	A mature ovum (egg)
Ovarian hyperstimulation syndrome (OHSS)	Systemic adverse effects from fertility drugs used for ovarian stimulation that can include bloating, ovarian enlargement, rapid weight gain, abdominal pain, vomiting, and respiratory, blood pressure, and metabolic complications
Ovulation	Release of an egg from one of the ovaries
Placenta previa	Implantation of the placenta over or near the cervix during the 2nd-3rd trimesters of pregnancy
Preeclampsia	Development of high blood pressure and protein in the urine during the 2nd-3rd trimesters of pregnancy
Preterm birth (PTB) / Preterm delivery	Preterm birth/delivery: birth/delivery at <37 weeks gestation; moderate preterm Birth/delivery = birth/delivery at <34 weeks gestation; early or very preterm birth/delivery = birth/delivery at <32 weeks gestation
Stillbirth	Death of the fetus at or after the 20th week of gestation

patient demand, limited resources, and uncertainty over clinical benefit in such populations, as well as reduce the healthcare costs associated with complications of pregnancy, delivery, and preterm birth/delivery (PTB/PTD), many healthcare systems have considered or introduced funding policies that include patient eligibility criteria. These eligibility criteria commonly relate to maternal age, body mass index (BMI), and smoking status (11–14). However, the extent to which these policies reflect the current clinical evidence is unclear.

METHODS

A recent environmental scan of patient eligibility criteria contained in IVF funding policies around the world was used to identify patient characteristics to be assessed (15). They were paternal age and maternal age, weight, and smoking. Relevant outcome measures (Table 2) were defined by an expert advisory committee, comprising general practitioners, reproductive endocrinologists, fertility specialists, gynecologists, neonatologists, and pediatricians.

A comprehensive search for papers published between January 2007 and June 2014 that explored the impact of these characteristics on the safety and effectiveness of IVF was then conducted in two stages. The first stage considered systematic reviews only. The second stage considered primary studies of patient characteristics and outcomes that were not addressed in the systematic reviews.

Identification of Relevant Papers

Stage 1: Systematic Reviews. To identify reviews, a structured search strategy, which combined relevant controlled vocabulary terms, such as Medical Subject Headings, with additional nonindex keywords was developed and applied to key bibliographic databases (see Supplementary Table 1 for the complete details and outputs of the search). To identify unpublished reviews, Google, gray literature databases, and Web sites were searched, along with Web sites of guidelines, clinical trials, health technology assessment agencies, and key assisted reproductive technology-related international and national organizations. Furthermore, the reference lists of relevant papers were scrutinized and clinical experts in Alberta were contacted.

Stage 2: Primary Studies. Because no reviews assessing the impact of maternal characteristics on pregnancy/delivery or neonatal/infant complications, maternal smoking on the rates of ovarian hyperstimulation syndrome (OHSS), cycle cancellation, or multiple pregnancy/births, or paternal age on the chances of multiple pregnancy/birth were found, a separate search for

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

Table 2. PICOS Elements of the Review Protocol

Parameter	Inclusion criteria	Exclusion criteria
Participants	• Couples 18 years of age and older with infertility	
Interventions	• IVF • ICSI	
Comparators	Population differences, including: • maternal and/or paternal age • maternal body size • maternal smoking	
Outcomes	Safety: • ovarian hyperstimulation syndrome (OHSS) • ectopic pregnancy • neonatal/infant complications (e.g., LBW, neonatal/perinatal mortality, birth defects, congenital malformations) • pregnancy and delivery complications (e.g., OHSS, ectopic pregnancy, preeclampsia, caesarean delivery, PTB/PTD) Effectiveness: • indicators of cycle success (e.g., number of oocytes retrieved, cycle cancellation) • pregnancy, miscarriage, live birth • multiple pregnancy/multiple birth	• Studies without any defined clinical outcomes
Study Design	• Systematic reviews	• Primary studies[a]

[a] Primary studies will be included if evidence gaps are identified after review of systematic reviews.

primary studies was conducted. A structured search strategy similar to that used for the systematic reviews was developed and applied to PubMed (Supplementary Table 1).

The titles and abstracts from both stages were screened independently by two researchers (A.N.;K.K.) using the inclusion/exclusion criteria listed in Table 2. Full-text articles retrieved were reviewed independently by the same two researchers for final inclusion/exclusion using the same criteria. Agreement between researchers was assessed using the kappa statistic (16). Disagreements were resolved through discussion and third-party review (TS).

Data Extraction and Critical Appraisal of Included Papers

Each researcher (A.N.;K.K.) independently extracted information from included reviews and studies using standard, pretested data abstraction forms and a set of decision rules (one for reviews and one for primary studies). The quality of each review was appraised using the Oxman and Guyatt index of scientific quality for systematic reviews (17;18). The quality of each primary study was assessed using the Oxford Levels of Evidence Scale (19). Where important details were missing from articles, the corresponding author was contacted for more information.

Synthesis of Extracted Information

Data extracted from reviews and primary studies were tabulated, to facilitate comparative analyses of the content and findings, and analyzed qualitatively. While a meta-analysis of reviews was planned, it could not be performed due to differences in inclusion/exclusion criteria across reviews and overlap between studies comprising reviews. Similarly, given the heterogeneity across included primary studies, a meta-analysis was not possible.

RESULTS

Overall Description of Included Reviews and Primary Studies

A total of 2,128 discrete citations were identified through the search for systematic reviews, of which, thirty-one potentially relevant reviews were selected for full assessment and ten for final inclusion (kappa = 0.92) (Figure 1). No reviews that assessed the impact of patient characteristic on neonatal/infant or pregnancy/delivery complications, paternal age on multiple pregnancy/birth, or maternal smoking on OHSS, cycle cancellation, or multiple pregnancy/birth were found (Table 3 and Supplementary Table 2). The search for primary studies yielded 7,181 discrete citations (Supplementary Figure 1), of which, seven were included (kappa = 1.00). Excluded studies and reasons for exclusion are listed in Supplementary Table 3. The outcomes of included studies are summarized in Supplementary Tables 4–12 (detailed methodological elements of each available upon request).

Maternal and Paternal Age

Parental age was assessed in four reviews of primarily retrospective cohort studies of fresh, autologous IVF/ICSI (intracytoplasmic sperm injection) with standard controlled ovarian

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

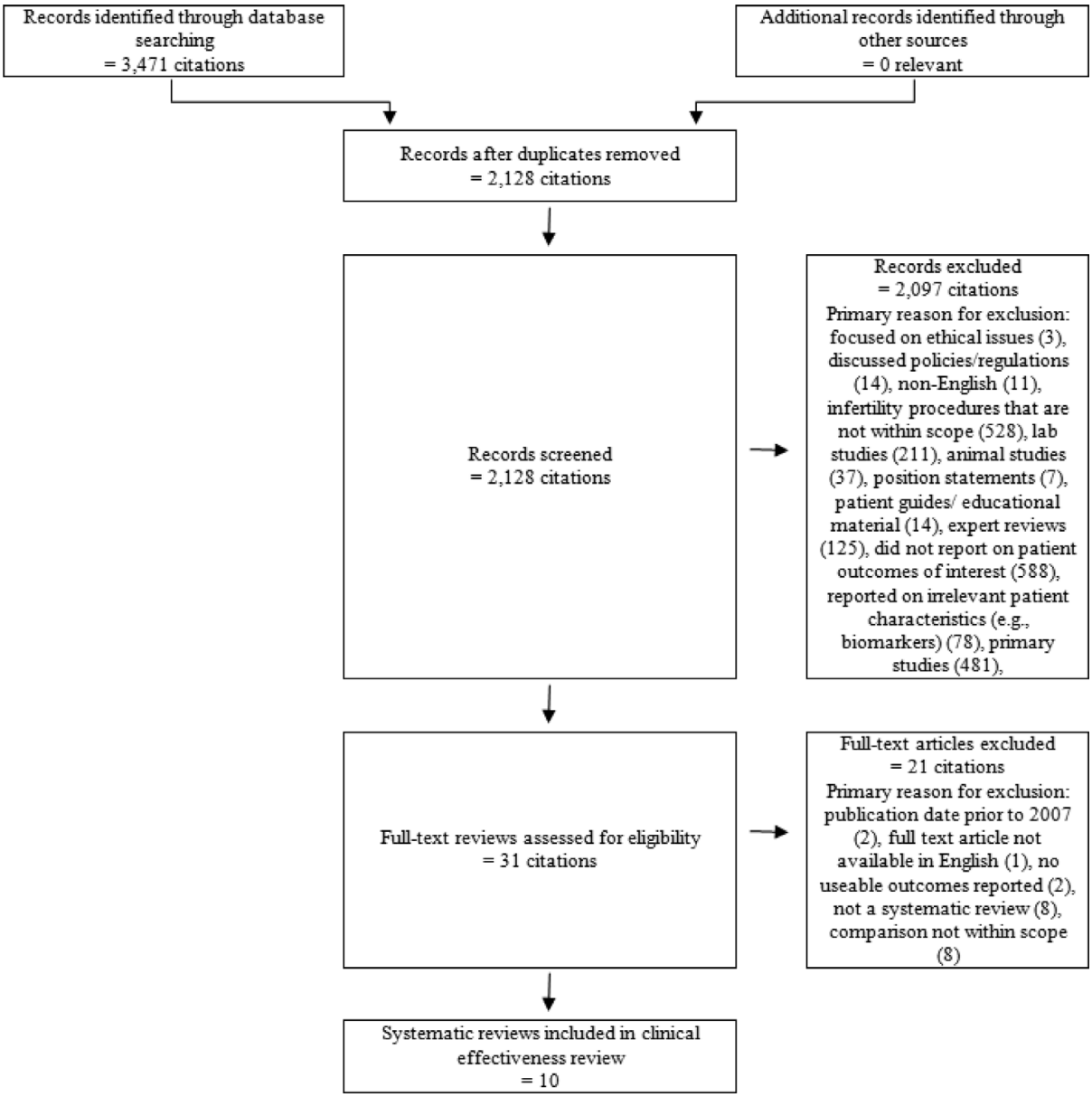

Figure 1. PRISMA flowchart of literature search results and study selection for clinical effectiveness review: systematic reviews.

stimulation (COS) protocols (20–23). Two reviews assessed the effect of paternal age on pregnancy, miscarriage and live birth, one of which also explored maternal age and reported cycle cancellation, OHSS, and ectopic pregnancy rates (20;21). The third considered the impact of maternal age on pregnancy (23). The fourth comprised a meta-analysis of individual patient data from randomized clinical trials (RCTs) that assessed the effect of single versus double embryo transfer, including a subgroup analysis by maternal age, on live and multiple births (22). No reviews evaluated the relationship between maternal or paternal age and obstetrical or neonatal/infant complications, or paternal age and multiple pregnancy/birth. Therefore, data were obtained from four additional primary studies (2012–2014): one retrospective cohort reporting birth defects in IVF/ICSI children among different maternal age groups and two retrospective cohorts and one prospective registry study assessing obstetrical complications after IVF/ICSI among women of different age groups (24–27). No additional primary studies assessing the effect of paternal age on the incidence of multiples, obstetrical complications, or neonatal complications were found.

Safety. One review assessing the effect of maternal and paternal age on OHSS and ectopic pregnancy rates following IVF/ICSI reported that, due to inadequate data, no conclusions could be made (20). A retrospective analysis of primary data on singleton deliveries following IVF/ICSI showed no significant difference in PTD between women <33 years of age and those ≥33, or women <36 and those ≥36 (27). However, a prospective IVF/ICSI registry study concluded that women under 40 were at a higher risk of PTB and delivering a low birth weight (LBW)

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

Table 3. Summary of Findings from Included Systematic Reviews and Primary Studies for Predefined Patient Characteristics and Outcomes of Interest

Outcome of interest	Increased maternal age	Increased paternal age	Maternal overweight / obesity	Maternal smoking
Effectiveness:				
• Cycle cancellation	Inconclusive	Inconclusive	Inconclusive	
• Pregnancy/live birth	Reduced	Inconclusive	Reduced	Reduced/no effect[a]
• Miscarriage	Increased	Inconclusive	Increased	Increased
• Multiple pregnancy/birth	No Effect		No Effect	
Safety:				
• OHSS	Inconclusive	Inconclusive	No effect	
• Ectopic pregnancy	Inconclusive	Inconclusive	No effect	Increased
• Pregnancy and delivery complications	Increased (PTB and LWB)		Increased (PTB, preeclampsia, hypertension, gestational diabetes)	
• Neonatal/infant complications	Inconclusive		Inconclusive	

Note. Blanks indicate no reviews or primary studies were found.
[a]Reduced pregnancy rates but not live birth rates.

baby than women 40 and older (24). The authors attributed this finding to an increased likelihood of multiple births in women under 40, regardless of the number of embryos transferred. Finally, a third primary study comparing women >49 years of age with those <43 found no differences in birthweight, gestational age at delivery, or obstetrical complications, such as preeclampsia, gestational hypertension, gestational diabetes, and preterm prolonged rupture of membranes (26).

Evidence related to the risk of malformations among offspring conceived through IVF/ICSI is limited. Birth defect rates by maternal age were reported in one primary study, which considered all women undergoing IVF/ICSI at a clinic in China (25). This study found similar birth defect rates among the offspring of women aged 21–30, 30–35, 36–40, and 41 and over.

Efficacy/Effectiveness. Across the reviews, reduced pregnancy and live birth rates, as well as increased miscarriage rates after IVF/ICSI were associated with higher maternal age (20;22;23). Specifically, pooled data from one review of mainly retrospective cohort studies indicated that for each 1-year increase in maternal age, the odds of a clinical pregnancy after a fresh IVF/ICSI cycle were significantly decreased by 4–6 percent, while disaggregated data from another review of mainly retrospective studies showed reduced chances of pregnancy in women over 38, 35, and even 30 years of age (20;23). In the most recent review, pregnancy rates were considerably lower in women >37 years of age (27 percent) compared with those <37 (45 percent) (20). They were also lower in women over 40–41 (3–9 percent), compared with those under 40–41 (17–28 percent), although statistical significance was not reported. A decline in the likelihood of live birth with increasing maternal age, particularly after age 40, was also seen (20). Moreover, a meta-analysis of eight RCTs found that the odds of a live birth after IVF/ICSI were 40 percent greater in women <33 years of age compared with those ≥33 years of age (odds ratio [OR], 1.4; confidence interval [CI], 1.1–1.8) (22).

In recent years, efforts to improve pregnancy and live birth rates in older women have included the use of IVF/ICSI with donor oocytes. A systematic review assessing donor IVF/ICSI suggested that pregnancy rates appeared to depend on the age of the oocyte donor, because rates were significantly lower in patients who received oocytes from donors 35–39 years old (32 percent) or >40 years old (23 percent) compared with those whose donors were 30–34 or <30 years of age (35–37 percent) (20). In contrast, rates of miscarriage and the number of cycles required to achieve a live birth were found to depend on the age of recipients. Higher rates of miscarriage and a greater number of cycles required to achieve a live birth were observed in older recipients (>36–40), even when the donor was young.

One review addressing paternal age reported a significant linear decline in semen volume with increasing paternal age (21). Most of the studies were retrospective cohorts or case-control studies reporting no significant age-effect on sperm concentration, motility, morphology, or implantation rates. However, some of these studies found that among men with oligozoospermia, the odds of an unsuccessful pregnancy increased by 5–11 percent for each 1-year increase in paternal age. In half of the included studies, live birth rates decreased with paternal age. One of those studies had adjusted for the type of infertility and the number of embryos transferred, reporting live birth rates of 38 percent, 17 percent, and 7 percent in women with male partners <35, 36–40, and >40 years of age, respectively. Furthermore, the proportion of women with a live birth after was significantly lower if the male partner was over 50 (41 percent) than if he was under 50 (56 percent; relative risk [RR], 1.5). Across most of the studies comprising the review,

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

no significant variations in miscarriage rates with paternal age were found. In the single meta-analysis that assessed the effect of maternal age on multiple birth rates, no association between age and likelihood of a multiple birth was found (22).

Maternal Weight

Five reviews, all of which included meta-analyses, evaluated the effect of maternal weight on the safety and effectiveness of IVF/ICSI (28–32). The reviews mainly comprised retrospective cohort studies of fresh, autologous IVF/ICSI cycles with a common COS protocol in unselected women or younger women (<35–44 years of age). One review also considered donor IVF/ICSI (32). All five reviews reported at least one measure of the effectiveness of IVF/ICSI, including cycle cancellation (one review), pregnancy, miscarriage and/or live birth (five reviews), and multiple pregnancy (one review) (28–32). Safety data were limited to the incidence of OHSS (two reviews) and ectopic pregnancy (one review) and were, therefore, supplemented by four additional primary studies (retrospective cohorts published 2012–2014) reporting pregnancy/delivery and neonatal complications (27;33–35).

In reviews and primary studies assessing the impact of BMI on the safety and effectiveness of IVF/ICSI, women with a BMI <20 were considered "underweight," 20–24.9 "normal" weight, 25–29.9 "overweight," 30–34.9 "obese," and ≥35 "morbidly obese." Many studies analyzed BMI at a cutoff of 25, comparing "underweight" or "normal" weight women (BMI <25) with "overweight," "obese," or "morbidly obese" women (BMI ≥25). Some studies used a BMI cutoff of 30 to compare "underweight," "normal" weight, or "overweight" women (BMI <30) with "obese" and "morbidly obese" women (BMI ≥30).

Safety. The two reviews that addressed the effect of maternal weight on the safety of IVF/ICSI demonstrated no differences in OHSS or ectopic pregnancy rates between "normal" weight or "underweight" women and "overweight" or "obese" women (28;31).

Across the four primary studies that examined the relationship between BMI and PTB, the incidence of PTB increased with BMI. In the most recent of these studies, BMI >30 was identified as a significant risk factor for PTB among singleton births after IVF/ICSI (27). Two of the studies presented retrospective analyses of a national IVF registry of over 80,000 IVF/ICSI births in the United States during different time periods. Both found that women whose BMI fell into one of three categories of increasing BMI cutoffs ("overweight," "obese," or "morbidly obese") had a statistically significantly higher likelihood of PTB, early PTB, and very early PTB in singleton births (33;35).The fourth study, a prospective cohort study, also reported a positive correlation between BMI and singleton PTB rate. In addition, statistically significantly more obstetrical complications, including preeclampsia, hypertension, and gestational diabetes, were noted among "morbidly obese" women (20 percent) than "normal" weight women (12 percent; $p < .05$). The number of cesarean deliveries performed was also greater in "obese" women (51 percent) than in "normal" weight women (36 percent; $p < .05$) (34). However, no statistically significant association between BMI and stillbirths, neonatal deaths, or birth defects was found.

With respect to twin births, the findings appeared to depend on the BMI cutoff applied. Statistically significantly higher rates of PTB were only observed in women with a BMI defined as "morbidly obese" (33;35).

Efficacy/Effectiveness. Findings from the five reviews examining the relationship between maternal weight and pregnancy and live birth rates after IVF/ICSI varied (29–32;36). In the first, neither clinical nor ongoing pregnancy rates differed with weight (28). However, in the second, which comprised a meta-analysis of twenty-five studies (mostly retrospective cohort studies), the likelihood of pregnancy in women with a "normal" weight was greater compared with that in women who were "overweight" or "obese" (RR, 0.9; $p < .05$) (29). In both of these reviews, women undergoing IVF/ICSI were significantly less likely to achieve a live birth if they were "overweight" or "obese" (OR, 0.8–0.9). In the third and earliest review (mostly retrospective cohort studies published 2000–2006), which included both biochemical and clinical pregnancies, pregnancy rates per woman were slightly lower in women with a BMI ≥25 than in women with a BMI <25 (OR, 0.81; CI, 0.67–0.98)) and were similar between women with a BMI ≥30 and <30 (31). Cycle cancellation rates per woman were higher in women with a BMI ≥30 compared with women with a BMI <30 ($p = .05$), but no significant differences were seen at a BMI cutoff of 25. Furthermore, in women with a BMI ≥25, the numbers of oocytes retrieved were significantly lower compared with women with a BMI <25, even with higher doses and durations of gonadotropin stimulation (OR, 0.58) (31). No significant differences in live birth rates were observed. One review specifically examined the effect of maternal BMI on the effectiveness of IVF/ICSI with donor embryos (32). In this review, no significant differences in pregnancy or live birth rates between "underweight," "normal" weight, "overweight," or "obese" women were observed (32).

In three reviews reporting miscarriage, "overweight" or "obese" women had a higher risk of miscarriage after IVF/ICSI compared with "normal" weight women (OR, 1.3–1.7) (29;31;36). However, when studies where age may have been a confounder were excluded, differences were no longer significant (30). In the only review reporting multiple births, pooled data from five studies showed no significant association with BMI (28).

Maternal Smoking Status

Pregnancy and live birth in women who were active smokers at the time of the IVF/ICSI procedure were compared with those in nonsmokers in a single review of prospective and

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

retrospective cohort studies (37). Most studies were limited to autologous IVF/ICSI and used common COS protocols. Safety data in this review were limited to ectopic pregnancy rates and no reviews reporting the effect of smoking on cycle cancellation rates or the incidence of multiples after IVF/ICSI were found. Furthermore, no additional primary studies examining the effect of smoking on cycle cancellation, multiple pregnancy/birth, or complications in IVF/ICSI patients were found.

Safety. Based on the findings of a single meta-analysis, the risk of experiencing an ectopic pregnancy was greater in women who were active smokers at the time of IVF/ICSI than in nonsmokers, even after age was taken into account (OR, 15.7) (37). No reviews or additional primary studies examining the effect of smoking on pregnancy/delivery complications were identified.

Efficacy/Effectiveness. Findings from the single meta-analysis of maternal smoking status suggested that women who were active smokers at the time of IVF were almost half as likely to become pregnant or achieve a live birth and over 2 times as likely to experience a miscarriage than nonsmokers ($p < .05$), regardless of whether they used their own oocytes or donor oocytes (37). However, after excluding studies where age was considered to be a confounder, only differences in pregnancy rates remained significant.

DISCUSSION

This review presents the state of the science regarding the impact of different patient characteristics on the outcomes of IVF/ICSI to inform public funding deliberations, including consideration of possible patient eligibility criteria emerging from published clinical evidence.

Over the past 7 years, several systematic reviews assessing the impact of patient characteristics on IVF/ICSI have been published. Because they vary in quality and scope, a systematic review of reviews was performed. There can be several limitations to performing reviews of reviews. The initial review may not provide enough details on the primary studies. Where important details were missing, the corresponding author of the review was contacted for more information and the primary studies comprising the reviews were retrieved. Reviews of reviews can also be limited by the questions addressed in each review, which may not provide relevant or enough information. Where gaps in the evidence obtained from systematic reviews were identified, we searched for additional primary studies to fill them.

Although the systematic reviews were of high quality, they primarily comprised observational studies, most of which did not control for potential confounders. Consequently, the validity of results is limited and should be interpreted conservatively. Nonetheless, they suggest that in IVF/ICSI patients, increased maternal age, weight, and smoking during pregnancy constitute risk factors for certain pregnancy/delivery and infant complications. Advanced maternal age was associated with lower likelihoods of pregnancy and live birth and a greater risk of miscarriage. While semen volume seems to decrease with paternal age, whether or not this translates into reduced reproductive function or poorer success with IVF/ICSI remains unclear. Therefore, before eligibility criteria can be based on paternal age, more studies investigating the effect of paternal age on the safety and effectiveness of IVF/ICSI after controlling for maternal factors are needed. Evidence related to maternal smoking status at the time of IVF/ICSI treatment suggests that although smoking lowers the probability of becoming pregnant, it has little impact on the probability of achieving a live birth.

Given the differences in the impact of smoking status across outcome measures, discussions around the relative importance of each of these outcomes are needed before smoking status can be legitimately incorporated into eligibility criteria. Obesity appears to be negatively associated with both pregnancy and live birth rates. Thus, published evidence related to the safety and effectiveness of IVF supports consideration of eligibility criteria around maternal age and morbid obesity to optimize maternal and infant outcomes. Implementing such criteria may reduce resources spent on ineffective treatment cycles and healthcare costs associated with complications. What the exact cutoff values for maternal age and BMI should be warrants further investigation. While PTB and LBW were increased in women >40 years of age, pregnancy rates were shown to decline with age starting as young as 30 years. Pregnancy rates were lower in women with a BMI of ≥25. Risk of PTB was higher at a BMI of 25 in singleton pregnancies and 35 in twin pregnancies. Future research should focus on the impact of each of these factors together and in combination with procedural characteristics that may modify these effects, such as the number of embryos transferred and the use of adjunct procedures in combination with IVF (e.g., ICSI and preimplantation genetic diagnosis).

An in-depth discussion around what is an acceptable level of clinical effectiveness of IVF in order for it to be publicly funded is needed. There are few socially insured services with a clinical effectiveness as low as 5 percent. The exception may be life-threatening conditions with no treatment alternatives. Thus, it may be argued that the opportunity costs of funding IVF for patients in whom the probability of achieving a healthy live birth is below a certain level are simply too large. It then becomes inequitable to patients with other diseases for which interventions that offer similar or greater levels of effectiveness remain unfunded.

CONCLUSIONS

Based on the evidence reviewed, it may be appropriate to consider incorporating eligibility criteria around maternal age and obesity in public funding policies in Canada and internationally to optimize the safety and effectiveness of IVF and reduce costs associated with complications and ineffective treatment cycles.

https://doi.org/10.1017/S0266462315000628 Published online by Cambridge University Press

To determine appropriate cutoff points, further research and a discussion around acceptable levels of clinical effectiveness are needed.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1–12
Supplementary Figure 1
http://dx.doi.org/10.1017/S0266462315000628

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Zegers-Hochschild F, Mansour R, Ishihara O, et al. International Committee for Monitoring Assisted Reproductive Technology: World report on assisted reproductive technology, 2005. *Fertil Steril*. 2013;101:366-378.
2. NICE. *Fertility: Assessment and treatment for people with fertility problems (update)*. Draft guidance for stakeholder consultation. London: RCOG Press / National Collaborating Centre for Women's and Children's Health for the National Institute for Health and Clinical Excellence (NICE); 2012.
3. Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining infertility-a systematic review of prevalence studies. *Hum Reprod Update*. 2011;17:575-588.
4. Evers JL. Female subfertility. *Lancet*. 2002 Jul 13;360:151-159.
5. Bushnik T, Cook JL, Yuzpe AA, Tough S, Collins J. Estimating the prevalence of infertility in Canada. *Hum Reprod*. 2012;27:738-746.
6. Ng EHY, Ho PC. Ageing and ART: A waste of time and money? *Best Pract Res Clin Obstet Gynaecol*. 2007;21:5-20.
7. Caplan AL, Patrizio P. Are you ever too old to have a baby? The ethical challenges of older women using infertility services. *Semin Reprod Med*. 2010;28:281-286.
8. Johnson JA, Tough S. Delayed child-bearing. *J Obstet Gynaecol Can*. 2012;34:80-93.
9. Balasch J, Gratacos E. Delayed childbearing: Effects on fertility and the outcome of pregnancy. *Fetal Diagn Ther*. 2011;29:263-273.
10. Balasch J. Ageing and infertility: An overview. *Gynecol Endocrinol*. 2010;26:855-860.
11. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: A review. *Hum Reprod Update*. 2007;13:209-223.
12. American Society for Reproductive Medicine. Smoking and infertility: A committee opinion. *Fertil Steril*. 2012;98:1400-1406.
13. CDC. Infertility FAQs. Atlanta, GA: Centers for Disease Control and Prevention (CDC); 2011. http://www.cdc.gov/reproductivehealth/infertility/ (accessed February 2013).
14. Dondorp W, de Wert G, Pennings G, et al. Lifestyle-related factors and access to medically assisted reproduction. *Hum Reprod*. 2010;25:578-583.
15. Dunn AL, Stafinski T, Menon D. An international survey of Assisted Reproductive Technologies (ARTs) policies and the effects of these policies on costs, utilization, and health outcomes. *Health Policy*. 2014;116:238-263.
16. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37-46.
17. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol*. 1991;44:1271-1278.
18. Oxman AD, Guyatt GH. The Oxman & Guyatt index of scientific quality [scoring system for systematic review]. Bandolier Professional 2003;(May):7.
19. Oxford Centre for Evidence-based Medicine levels of evidence and grades of recommendation [internet]. Oxford, UK: Oxford Centre for Evidence-based Medicine (CEBM); 2011. http://www.cebm.net/ocebm-levels-of-evidence/ (accessed February 2013).
20. Watt AM, Elshaug AG, Willis CD, Hiller JE. Assisted reproductive technologies: A systematic review of safety and effectiveness to inform disinvestment policy. *Health Policy*. 2011;2-3:213.
21. Dain L, Auslander R, Dirnfeld M. The effect of paternal age on assisted reproduction outcome. *Fertil Steril*. 2011;95:1-8.
22. McLernon DJ, Harrild K, Bergh C, et al. Clinical effectiveness of elective single versus double embryo transfer: Meta-analysis of individual patient data from randomised trials. *BMJ*. 2010;341:c6945.
23. van Loendersloot LL, van Wely M, Limpens J, et al. Predictive factors in in vitro fertilization (IVF): A systematic review and meta-analysis. *Hum Reprod Update*. 2010;16:577-589.
24. Lawlor DA, Nelson SM. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: A prospective study. *Lancet*. 2012;379:527.
25. Yan J, Wu K, Tang R, Ding L, Chen ZJ. Effect of maternal age on the outcomes of in vitro fertilization and embryo transfer (IVF-ET). *Sci China Life Sci*. 2012;55:694-698.
26. Kort DH, Gosselin J, Choi JM, et al. Pregnancy after age 50: Defining risks for mother and child. *Am J Perinatol*. 2012;29:245-250.
27. Ban Frangez H, Korosec S, Verdenik I, et al. Preterm delivery risk factors in singletons born after in vitro fertilization procedures. *Eur J Obstet Gynecol Reprod Biol*. 2014;176:183-186.
28. Koning AM, Mutsaerts MA, Kuchenbecher WKH, et al. Complications and outcome of assisted reproduction technologies in overweight and obese women. *Hum Reprod*. 2012;27:457-467.
29. Rittenberg V, Seshadri S, Sunkara SK, et al. Effect of body mass index on IVF treatment outcome: An updated systematic review and meta-analysis. *Reprod Biomed Online*. 2011;23:421-439.
30. Waylen AL, Metwally M, Jones GL, Wilkinson AJ, Ledger WL. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: A meta-analysis. *Hum Reprod Update*. 2009;15:31-44.
31. Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology–A systematic review. *Hum Reprod Update*. 2007;13:433-444.
32. Jungheim ES, Schon SB, Schulte MB, et al. IVF outcomes in obese donor oocyte recipients: A systematic review and meta-analysis. *Hum Reprod*. 2013;28(10):2720-2727.
33. Dickey RP, Xiong X, Gee RE, Pridjian G. Effect of maternal height and weight on risk of preterm birth in singleton and twin births resulting from in vitro fertilization: A retrospective cohort study using the Society for Assisted Reproductive Technology Clinic Outcome Reporting System. *Fertil Steril*. 2012;97:349-354.
34. Zander-Fox DL, Henshaw R, Hamilton H, Lane M. Does obesity really matter? The impact of BMI on embryo quality and pregnancy outcomes after IVF in women aged ≤38 years. *Aust N Z J Obstet Gynaecol*. 2012;52:270-276.
35. Dickey RP, Xiong X, Xie Y, Gee RE, Pridjian G. Effect of maternal height and weight on risk for preterm singleton and twin births resulting from IVF in the United States, 2008–2010. *Am J Obstet Gynecol*. 2013;209:349e1–6.
36. Somigliana E, Vercellini P, Daguati R, et al. Fibroids and female reproduction: A critical analysis of the evidence. *Hum Reprod Update*. 2007;13:465-476.
37. Waylen AL, Metwally M, Jones GL, et al. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: A meta-analyis. *Hum Reprod Update*. 2009;15:31-44.