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Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

Controversies in assisted reproduction – Multiple choice answers Vol. 53

1. a) F b) F c) F d) T e) T

Current evidence suggests there is no increase in the risk of congenital birth defects compared to IVF controls although larger scale trials are needed. Imprinting errors are not increased in embryos derived from IVM compared to those from standard IVF controls for the target genes LIT1, SNRPN, PEG3 and GTL2. Most studies have found no difference in developmental milestones in children from IVM treatment compared to either IVF controls. However, one study involving a cohort of French children born following IVM treatment, found that at birth, female infants in the IVM treatment group displayed increased weight, height, BMI and head circumference compared to IVF controls and at two years of age, weight and BMI remained significantly higher. This finding may be a cause for concern and further evidence is needed for the safety of IVM in this regard. Embryo aneuploidy rates following IVM in human studies appear to be the same as for their in vivo controls. Elevated aneuploidy rates were observed between IVM and IVF embryos; however, the increased rates of chromosomal aneuploidy only resulted following longer periods of maturation timing, with no elevated rates of aneuploidy following 24 hours maturation but increased rates following 40 hours. The risk of miscarriage is significantly increased following IVM, although it is part attributed to the predominantly PCOS patient population rather than the treatment method itself. However, most of the literature involving IVM outcomes involve fresh embryo transfers where asynchrony between embryo and endometrial development is likely to be problematic. Frozen embryo transfers following IVM do not report the same elevated risk of miscarriage.

2. a) T b) T c) F d) T e) T

A patient with an AMH of >100 pmol/l. and an antral follicle count of >20 indicates a potential diagnosis of PCOS and needs to be investigated and diagnosed according to the Rotterdam criteria. Such a patient would be an ideal candidate for IVM treatment as PCO/PCOS patients demonstrate higher success rates compared to non- PCOS controls. A high antral follicle count is a determinant of IVM success and they will have no risk of OHSS compared to an elevated risk from standard IVF. IVM is a successful treatment option for fertility preservation in patients prior to breast cancer treatment. IVM provides a number of benefits to this patient population including minimising levels of circulating oestrogen due to the reduced or eliminated gonadotrophin administration, eliminating the risk of OHSS and allowing patients to progress immediately to chemo/radiotherapy. IVM is currently not recommended for patients with a decreased ovarian reserve. As an elevated antral follicle count is one of the determining factors for IVM treatment success and these patients will have a reduced antral follicle count, standard IVF treatment is recommended for these patients. IVM remains the only treatment method to eliminate the risk of OHSS and has proven successful in patients at an increased

risk of the condition; therefore IVM is a suitable treatment alternative for this subset of patients. Successful ex-vivo oocyte collection and in-vitro maturation has now been reported from a number of case studies, including cases involving additional ovarian tissue cryopreservation, has led to live births.

3. a) F b) F c) F d) T e) F

Early animal studies determined that extended time in maturation culture results in hardening of the zona pellucida and therefore, it was believed that ICSI would be a necessary insemination technique for IVM oocytes. However, as maturation timings have reduced in recent years and with the development of improved IVM culture systems and protocols, IVF as an insemination technique in IVM has been shown to be effective. Recent studies involving sibling oocytes demonstrated no statistically significant differences between IVF and ICSI insemination rates for IVM oocytes. IVM has been performed successfully without the use of any hormonal priming in a number of studies, with oocytes retrieved at the GV stage from very small follicles and successful pregnancies and live births ultimately being achieved. However, increased success rates have been reported using short, low dose FSH or hMG priming and no ovulation trigger. Patients with PCOS are the target presentation for IVM treatment having elevated antral follicle counts and the subsequent risk of OHSS making them ideal candidates. Additionally, the high AFC maximises the oocyte yield at TVOA. However, IVM should not be limited to treating PCOS patients as case reports in the literature have demonstrated that IVM can be used to treat unique presentations including for fertility preservation in cancer patients and for patients with resistant ovary syndrome. With the emergence of time lapse incubation systems, continuous monitoring and recording of stage specific events, it has led to the conclusion that IVM embryos often display higher levels of abnormal embryo cleavage patterns and aberrant embryo development. While IVM is often suggested to be a cost conservative treatment, to date, there is no evidence of a cost benefit analysis.

4. a) F b) F c) T d) F e) F

Chromosomal abnormalities in the fetus are generally caused by an error in cell division during gametogenesis. If fertilisation should happen between gametes where one or both contain a chromosomal abnormality, then there is an increased risk of the fetus inheriting that abnormality. Although there is some evidence that sperm chromosomal abnormalities increase with male age, there is little evidence that male age influences sperm DNA fragmentation. Moreover, sperm chromosomal abnormalities and sperm DNA fragmentation do not correlate. There is no evidence that monozygotic or dizygotic twinning is related to sperm DNA fragmentation. Several studies have shown a correlation between sperm DNA fragmentation and the risk of early pregnancy loss (miscarriage). There is currently no evidence that sperm DNA fragmentation has any relationship with the risk of pre-term birth. Although there is some evidence that soluble components of seminal plasma and/or semen microbes can alter the risk of pre-eclampsia, there is no evidence that sperm DNA fragmentation plays a role.

5. a) T b) T c) F d) T e) F

Studies have shown that men infected with *Chlamydia trachomatis* have greater levels of sperm DNA fragmentation than men with no infection and that this will improve following antibiotic therapy. The mechanism appears to be that the bacterium triggers apoptotic pathways in sperm which leads to premature sperm death. Recovery of motile sperm by Density Gradient Centrifugation (DGC) leads to a population of sperm with lower levels of sperm DNA fragmentation. This is not because DGC repairs or alters sperm DNA, rather it preferentially isolates those sperm with more intact DNA. Reducing ejaculatory frequency is not compatible with lowering the proportion of sperm with DNA fragmentation. When ejaculation does not occur, sperm which are stored in the vas deferens begin to be mixed with new sperm leaving the epididymis. This increases the level of sperm DNA fragmentation as the new sperm are damaged by free radicals generated by older senescent sperm. This phenomenon has been

poorly studied but it is likely that each male will have an optimum abstinence period which leads to an ejaculate with this lowest proportion of sperm with DNA fragmentation. There is some evidence that sperm DNA integrity can improve following varicocelectomy which implies that sperm DNA fragmentation is increased in men with a varicocele. However, there is currently no consensus about how to select which men may benefit from varicocelectomy or which is the most appropriate surgical technique to use. Although there is data to show that men who wear tight underwear are at increased risk of ejaculating samples with a low motile sperm counts there is no current evidence that tight underwear causes sperm DNA fragmentation. Moreover, in a recent study there was no relationship between choice of underwear and time to pregnancy.

6. a) T b) T c) F d) F e) T

The Sperm Chromatin Structure Assay was one of the first laboratory tests developed to measure sperm DNA fragmentation and uses a flow-cytometer to measure the susceptibility of sperm DNA to damage under the conditions generated in the assay. TUNEL stands for terminal deoxynucleotidyl transferase dUTP nick end labelling and is a test which directly identifies the broken parts of sperm DNA by attaching a probe or label to the damage. The hypo-osmotic swelling test is a test which measures the viability of sperm by assessing the ability of live sperm to swell when placed in a hypo-osmotic solution. It does not assess sperm DNA fragmentation. Magnetic Activated Cell Sorting (MACS) is a generic laboratory technique which can isolate specific cells using antibodies attached to magnetic beads. It can be used to remove sperm undergoing apoptosis by using an antibody which recognises phosphatidylserine but it is not in itself a test of sperm DNA fragmentation. The Sperm Chromatin Dispersion Test is similar to the Sperm Chromatin Structure Assay (SCSA) in that it measures the susceptibility of sperm DNA to damage under the conditions generated in the assay. It is based on the principle that sperm with fragmented DNA fail to produce a characteristic halo of dispersed DNA loops that is observed in sperm with non-fragmented DNA, following acid denaturation and removal of nuclear proteins.

7. a) F b) F c) F d) T e) F

The American Society for Reproductive Medicine published reports in 2006, 2008 and 2011 which stated that “current methods for evaluating sperm DNA integrity do not reliably predict treatment outcomes”. In 2013 the British Fertility Society concluded that “sperm DNA damage appears to be related to sperm quality, embryo development and pregnancy loss, yet there remains no consensus on the best testing procedures, clinical reference values and how patients with an adverse result should be managed”. In 2011, a special interest group of the European Society for Human Reproduction and Embryology (ESHRE) concluded that whilst “impaired sperm DNA integrity may have the greatest effect (and hence, greatest clinical utility) on IUI pregnancy rates and on pregnancy loss following IVF and ICSI, larger (adequately powered), properly designed and controlled prospective studies are absolutely required to confirm these results. Neither the World Health Organization laboratory manual for the Examination and processing of human semen or a recent Evidence Synthesis Group make any recommendation about testing for sperm DNA fragmentation. In 2017 the Society for Translational Medicine concluded that “sperm DNA fragmentation testing is recommended in patients with clinical varicocele and borderline to normal semen parameters as it can better select varicocelectomy candidates” and “infertile men with modifiable lifestyle factor may benefit from sperm DNA fragmentation testing by reinforcing risk factor modification and monitoring patient’s progress to intervention”.

8. a) F b) F c) T d) T e) T

Many technical limitations contributed to the failure of early PGT-A trials to show improved pregnancy outcomes. FISH is only able to detect aneuploidy involving the chromosomes tested (13, 18, 21, X, Y), and the accuracy per probe is 92–99% resulting in a high overall error rate. Cleavage-stage embryos have high rates of embryonic mosaicism, and mosaicism is not identified with a single

blastomere biopsy. Therefore, an aneuploidy diagnosis resulting from a single blastomere, would exclude a potentially viable embryo from transfer. Cleavage-stage blastomere biopsy is associated with a 39.1% relative reduction in implantation rate, presumably due to harm from the biopsy procedure.

9. a) T b) F c) T d) T e) F

qPCR does not utilize WGA. Multiplex PCR amplification is performed on 96 selected loci spread throughout the genome (4 per chromosome). Due to select amplification of certain loci, qPCR has limited detection for triploidy, and does not detect unbalanced translocations, partial aneuploidies, or mosaicism.

10. a) T b) T c) F d) F e) F

Mosaic trisomies 13, 14, 16, 18, 21, 45 and X should not be considered for transfer due to a high risk of fetal involvement and/or risk of fetal syndromes. Those with the lowest risk with transfer (composite score of 0) are mosaic trisomies 1, 3, 10, 12, and 19. Those with a composite score of 1 are mosaic trisomies 4 and 5 and 47, XYY. A composite score of 2 was assigned to mosaic trisomies 2, 7, 11, 17, and 22, a composite score of 3 to mosaic trisomies 6, 9, and 15, and a composite score of 4–5 to mosaic trisomies 8, 20, 47, XXX, and 47, XXY.

11. a) T b) T c) F d) T e) T

Extended embryo culture to the blastocyst stage helps to select for euploid embryos. In studies comparing euploidy rates between patients undergoing cleavage-stage blastomere biopsy and blastocyst-stage TE biopsy, the average total number of euploid embryos per retrieval cycle were the same between groups, but the percentage of euploid embryos were higher in the blastocyst biopsy group than in the cleavage-stage biopsy group (42% vs 24%). Studies of 24-chromosome PGT-A have shown improved implantation rates and decreased miscarriage rates. Single embryo transfer with PGT-A reduces multiple gestations.

12. a) T b) T c) F d) T e) T

Polycystic ovarian syndrome (PCOS) is a heterogeneous condition. Features of PCOS may include menstrual cycle disturbance, hyperandrogenism and obesity. All of the listed condition can present with menstrual disturbance.

13. a) T b) T c) T d) F e) T

Hydrosalpinx is essentially the collection of fluid in the fallopian tube due to a spectrum of pathology resulting in distal tubal occlusion and tubal dilatation. *Chlamydia trachomatis* is the most common pathogen to cause tubal infection. Infertility following pelvic inflammatory disease is usually due to tubal blockage which may be proximal or distal. Westrom et al. reported a 10–15% incidence of infertility after one episode of PID, 20–25% incidence following two episodes and 50–55% incidence after three episodes. Numerous studies have reported on the poor outcome of IVF in patients with hydrosalpinges. Different theories have been proposed as to why hydrosalpinges adversely affect success rates including the possible wash out of the embryo by the hydrosalpingeal fluid flowing through the endometrial cavity. Secondly it is suggested that the hydrosalpingeal fluid itself is embryotoxic and thirdly that the hydrosalpingeal fluid may cause endometrial alterations rendering it hostile to embryo implantation. Hydrosalpinx in post-menopausal women is rare. It is important to bear in mind the possibility of primary ovarian malignancy with fallopian tube involvement or primary fallopian tube carcinoma in post-menopausal women with ultrasound confirmation of a hydrosalpinx.

14. a) F b) F c) T d) T e) T

Congenital uterine anomalies are thought to occur as a result of incomplete development of one or both müllerian ducts (uterine agenesis, unicornuate uterus), incomplete fusion of the ducts (uterus didelphys, bicornuate uterus) or failure of regression of the midline septum that forms during the unification of the two ducts (septate uterus). Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH) involves uterine agenesis; fertility treatment options include surrogacy as the ovaries are functioning in terms of hormone production and oocytes. An alternative option includes uterine transplantation. Metroplasty is no longer recommended for uterine didelphys and bicornuate uterus. Single embryo transfer is recommended for women with a bicornuate uterus as women with uterine anomalies have an increased risk of cervical incompetence and in addition to a smaller sized uterine cavity are at increased risk of preterm labour. It is recommended that women with uterine anomalies when pregnant have serial ultrasound scans monitoring cervical lengths and assessing fetal growth. Uterine anomalies may also be associated with renal abnormalities. Embryologically, the genital system develops in close association with the urinary system.

15. a) T b) F c) T d) T e) T

The prevalence of obesity as a worldwide epidemic has increased significantly over the past decade. Several studies have confirmed that obesity impairs ovarian responsiveness to gonadotropin stimulation (increased duration, amount of gonadotropin administered, cycle cancellation, decreased oocytes retrieved). Studies have shown that overweight or obese women have a higher rate of miscarriage compared with normal-weight women. Delaying pregnancy until 1–2 years after bariatric surgery has been recommended to avoid fetal exposure to nutritional deficiencies from rapid maternal weight loss. Orlistat decreases absorption of fat-soluble vitamins, primarily vitamin D, so that supplementation with a multivitamin containing vitamin D, administered at least 2 hours before or after orlistat ingestion, is recommended. Gastrointestinal side effects are common. Contraindications for the use of orlistat include chronic malabsorption syndromes and cholestasis.

16. a) T b) T c) T d) T e) T

Endometrial cavity fluid is reported to occur during controlled ovarian stimulation in approximately 5% of IVF cycles. The implantation and pregnancy rates are lower if endometrial cavity fluid is associated with hydrosalpinx, if endometrial cavity fluid is present on the day of embryo transfer or if the volume of the cavity fluid is large. The aetiology of endometrial cavity fluid may be attributed to reflux from a hydrosalpinx.

17. a) T b) T c) T d) F e) F

Immotile sperm may still be viable. Viability tests for immotile sperm include the hypo-osmotic swelling test. It is recommended that azoospermic men have Y chromosome micro-deletion studies. There are three loci for deletions in the region Yq11 and they are named AZFa, AZFb and AZFc. All these microdeletions may be detected by PCR. In men with AZFc deletions, either azoospermia or severe oligozoospermia may be present. Testicular histology in these patients shows varying stages of maturational arrest but there may be a few tubules that contain mature sperm. It is possible to treat men successfully with very small numbers of sperm in either their ejaculate or in their testicular tissue using ICSI. Men should be informed that these microdeletions may be transmitted to a male fetus. Men regularly using anabolic steroids such as athletes and weightlifters in an effort to increase muscle bulk may present with hypogonadotrophic hypogonadism and infertility. The serum levels of FSH, LH and testosterone are very low. Suppression of gonadotrophin secretion by anabolic steroids can be profound and persist for many months or years following their discontinuation. Klinefelters syndrome is the most common sex chromosomal abnormality seen in an infertility clinic. The white cell karyotype shows the presence of a 47, XXY configuration. The phenotype associated with this condition includes

signs of hypoandrogenism, decreased beard growth and reduced libido. Gynaecomastia may be present and testicular size is reduced. Serum levels of gonadotrophins are raised and serum testosterone is either in the lower range of normal or is reduced. It is possible to retrieve sperm from testicular biopsies from men with Klinefelters syndrome and with the use of ICSI pregnancies have been achieved. Globozoospermia is a well-known but rare condition where the sperm head lacks the acrosome. Fertilisation and pregnancies can be achieved with ICSI.

18. a) T b) T c) T d) T e) F

In women of childbearing age, hyperprolactinaemia commonly presents with oligo-menorrhoea, loss of libido or galactorrhoea. The causes of hyperprolactinaemia can be classified as physiological, pharmacological or pathological. As physiological causes pregnancy and lactation are the most common causes. Many medications cause hyperprolactinaemia by inhibition of dopamine synthesis or by blocking endogenous dopamine receptors. These medications include antidepressants, antiemetics and antipsychotics. An association has been demonstrated between ergot-derived dopamine agonist use and valvular heart disease in patients treated for Parkinson's disease. This raised concern amongst endocrinologists about the safety of long term treatment with bromocriptine and cabergoline in patients with hyperprolactinaemia. Most endocrinologists recommend monitoring with echocardiography for patients requiring treatment with cabergoline or bromocriptine long term. Studies have shown that the incidence of miscarriages, ectopic pregnancies or congenital malformations is no higher in infants born to mothers who conceived while taking bromocriptine than in the general population. Cabergoline has also been shown to be safe but it is less extensively studied. However, it is recommended that dopamine agonists be stopped once a positive pregnancy test is obtained.

19. a) T b) T c) F d) T e) F

Auto-grafting of ovarian tissue is done when the patient is in remission, age appropriate and ready to start a family. The tissue is transplanted in the orthotopic position (into its natural site e.g. ovarian hilum or nearby structures such as the broad ligament or pelvic sidewall). This may offer the potential for spontaneous pregnancy without requiring IVF. Heterotopic transplantation (ectopic location) e.g. arm has certain advantages such as easier follicular monitoring and egg retrieval for IVF and closer monitoring for cancer recurrence following auto-grafting. Orthotopic transplantation has been shown to result in less follicle loss and more effective re-vascularization. Pelvic irradiation increases the risk of pregnancy-related complications, including spontaneous miscarriage, preterm labour, low birthweights, and placental abnormalities. This is most likely due to a reduced uterine volume, impaired uterine distensibility due to myometrial fibrosis, uterine vascular damage and endometrial injury. The degree of uterine damage depends on the total radiation dose, site of irradiation, and patient age at time of treatment. The pre-pubertal uterus is more vulnerable than the adult uterus. Conventional ovarian stimulation results in supra-physiological serum oestradiol levels that may have an adverse effect, encouraging the re-growth of breast tumour cells. Use of aromatase inhibitors in addition to FSH limits the serum oestradiol rise. A typical regimen can be 5.0mg/day of letrozole throughout the entire period of controlled ovarian stimulation. In addition, in antagonist cycles using GnRH agonist for final oocyte maturation can decrease post-trigger oestradiol exposure. There are 2 methods of cryopreservation: slow freezing and vitrification. The standard method for cryopreservation of ovarian tissue has been slow freezing. Several reports have shown improved outcomes after vitrification of ovarian tissue as compared to the slow freezing technique in preserving granulosa cells and ovarian stroma, but outcome studies are warranted before vitrification replaces slow freezing as the standard method of ovarian tissue cryopreservation. The main concern with ovarian tissue banking is the possibility of re-seeding a tumour, harboured within the ovarian slices after auto-grafting the frozen-thawed tissue slices. Tissue samples are carefully screened for the presence of malignant cells (micro-metastases) by histology and specific immune-histochemical or molecular tests such as polymerase chain reaction (PCR) testing and real-time PCR to detect molecular markers that would indicate presence of cancer cells. Low risk groups for ovarian tissue micro-metastasis include Non-Hodgkins lymphoma and breast

cancer stage 1–111. The moderate risk group include upper GI system malignancies and the high risk group includes Leukaemia, Burkitts lymphoma and neuroblastoma.

20. a) T b) T c) F d) T e) T

Amiodarone is an anti-arrhythmic medication used to treat and prevent a number of types of irregular heartbeats including ventricular fibrillation. Amiodarone may induce both hyperthyroidism and hypothyroidism. Grave's disease is the most common cause of hyperthyroidism in pregnancy. The transplacental passage of TSH receptor antibodies may cause fetal and/or neonatal hyperthyroidism while antithyroid drugs can induce fetal hypothyroidism. Anti-thyroid medications include carbimazole and propylthiouracil. There has been an association between carbimazole and the rare benign scalp condition of aplasia cutis, oesophageal atresia, choanal atresia and dysmorphic facial features in the fetus. Propylthiouracil has not been associated with teratogenicity and both medications demonstrate no significant differences in their propensity to induce fetal hypothyroidism. As a result propylthiouracil is the medication of choice when planning a pregnancy. A clinical practice guideline has recommended that in women with pre-existing hypothyroidism, the TSH level should be kept below 2.5 mU/L before embarking on pregnancy. Thyroxine requirements are known to increase in the majority of cases in the first trimester and when pregnant thyroxine doses should be increased by 4–6 weeks gestation. A further guideline recommends that at the diagnosis of pregnancy, thyroxine should be increased by 25 or 50 µg. Thyroid function should ideally be tested preconception, at the diagnosis of pregnancy, at antenatal booking and monitored at least once in each trimester of pregnancy. As in pregnancy, thyroxine requirements are also increased with controlled ovarian stimulation during assisted reproduction. In hypothyroid women already taking thyroxine treatment, the thyroxine dose should be increased at the start of ovarian stimulation and as soon as pregnancy is confirmed. The major side-effect of drug therapy for hyperthyroidism is agranulocytosis. It occurs in approximately 1 in 1000 patients and usually occurs within 3 months of commencing treatment. All patients should be counselled regarding the importance of seeking medical advice if they develop an unexplained fever or sore throat. The attending physician should organize a white blood cell count. Rashes may also occur and the drug should be changed.

21. a) T b) T c) F d) T e) F

The prognosis for success after microsurgical vasectomy reversal declines progressively as the interval between vasectomy and its reversal increases. Metformin is an insulin-sensitizing medication that is commonly used for treating type 2 diabetes. There is evidence to suggest that metformin decreases the risk of OHSS in PCOS patients. There is good evidence available not to recommend bed rest following embryo transfer. Side-effects of metformin include anorexia, epigastric discomfort and diarrhoea. Lactic acidosis has occurred in patients with severe hepatic or renal disease and metformin is contraindicated in these patients. Metformin should be discontinued prior to intravascular administration of iodinated contrast agent because of the risk of renal failure and subsequent lactic acidosis. Restart no earlier than 48 hours after the test of renal function has shown no deterioration. As the corpus luteum produces oestrogen in addition to progesterone, studies have investigated the benefit of adding oestradiol to progesterone for luteal support in IVF. A meta-analysis of four RCTs addressing this subject has, however, suggested that the addition of oestrogen to progesterone in the luteal phase of IVF cycles does not improve pregnancy rates.

22. a) F b) T c) F d) F e) T

Following the report 'One Child at Time: Reducing Multiple Births after IVF the HFEA set multiple birth rate targets to promote eSET. The ultimate target was set at 10%. The HFEA set a target of 10%. Centres licenced by the HFEA had to reach this target by 2012.

23. a) T b) T c) F d) F e) T

The process of vitrification first includes exposure to cryoprotectants following by rapid cooling. Cooling rates for vitrification can reach $-30,000\text{ }^{\circ}\text{C}/\text{min}$ or higher. Vitrification involves increasing the viscosity during cooling in order for the liquid phase to chase to a vitreous 'glassy' state. Decreasing the chance of ice crystal formation improves survival rates. Lower concentrations of cryoprotectants are used with controlled slow rate freezing. This is a disadvantage of vitrification as the high concentrations of cryoprotectants that embryos are exposed to during vitrification could have a toxic effect. Both permeating and non-permeating cryoprotectants are required to maximise survival. Vitrification is both time and temperature dependent and requires high technical skill. A robust training programme should be in place to ensure good survival rates are achieved.

24. a) F b) T c) F d) F e) T

A blanket policy may have a significant adverse effect on pregnancy rates so a targeted approach was introduced. The legislation mandates, regardless of embryo quality, the transfer of a maximum of one embryo in the first and second cycles in women under the age of 35 (and two embryos for subsequent cycles), and a maximum of two embryos in women 35 years or older. The legislation used a cut off of age 35 for mandatory eSET. Although embryo quality is a predictor of outcome the legislation in Turkey does not take into account embryo quality. A maximum of two embryos can be replaced in women 35 years or older.

25. a) F b) T c) T d) T e) F

The UK saw a change in practice in 2004 with the maximum number of embryos replaced being reduced from 3 to 2 in patients under 40. The policy still allowed women over the age of 40 to have a maximum of 3 replaced. The policy reduced the number of twin pregnancies but failed to reduce the increasing number of twin pregnancies. The policy set a maximum of 2 embryos to be replaced in women over 40. The concept of eSET was not introduced until after the 2005 commissioned report 'One Child at a Time: Reducing Multiple births after IVF'.

26. a) F b) T c) F d) F e) F

The CDC is a federally funded research organization that also engages in disease prevention and interception under the direction of the US Federal government. It is not a regulatory agency. CDC collects outcomes data from all US clinics, including egg donation outcomes, under the Clinics Reporting Act of 1992 but plays no regulatory role. The FDA is the only Federal agency with current regulatory authority over egg donation procedures. The FDA regulations for egg donation fall under section 1271, the regulation of human tissue and tissue banks. The FDA has the ability to levy fines and shut fertility clinics who fail to comply with the FDA regulations. SART is an industry support organization and has no legal regulatory authority over fertility clinics or egg donation programs. SART is a subdivision of the American Society for Reproductive Medicine (ASRM) and receives financial support from both ASRM and individual member clinics. Not all fertility clinics report their outcomes to SART, and there is no obligation to do so. The Federal Penal Code is the register of all Federal Statutes, approved by acts of Congress and enforced by the Executive Branch and its agencies. In the US, Federal law supersedes all State laws, but there is no federal law regulating egg donation. Each State within the US has an agency for administration of state supported health care. Several states have regulated egg donation through legislation and administer the regulations through their penal codes, but none of them regulate egg donation through their HHS departments.

27. a) F b) F c) T d) F e) F

There are a handful of States that have laws promoting egg donation for fertility care only. No State has legislation that promotes donor compensation for eggs intended for research. The most recent attempt to rectify this difference passed through the California State Assembly only to die in committee. Many states forbid 'valuable consideration' for egg donation but allow compensation for the donor's time. None of these states has defined 'valuable consideration', so it is technically possible to pay the donor any 'hourly rate' without restriction. Two states continue to have explicit caps on egg donor compensation; Indiana and Arizona. No State has any law that defines a standard for donor compensation, and it would likely be a violation of the American Constitution's 14th amendment to, on the basis of ethnicity, treat people differently under the law. No recorded legislation in any American State designates a limit on compensation to an egg donor based on a price 'per egg'. If anything, states with restrictive legislation tend to prohibit the 'sale of eggs'.

28. a) F b) F c) F d) F e) T

Egg donation agencies and their donors may reside outside a restricted jurisdiction but the clinic may still not compensate the donor, 'part-time', or not, in the restricted jurisdiction. A cash payment to the donor may go undetected if there is no electronic 'money trail'. Though possible to engage in this sort of activity, it would still be a violation of the anti-compensation statute. It would also possibly be a violation of American tax law if the donor fails to declare the payment on her tax returns or the clinic fails to account for it. A local egg bank could not exist in a state with absolute restriction against compensation for egg donation. Even more than clinics that recruit and screen their own donors, egg banks are clearly transacting over eggs, making it legally impossible to establish a functional egg bank in a State that forbids egg donor compensation. A donor who was a resident of a jurisdiction that forbade compensation for egg donation could 'work' out-of-state, receive compensation for her donation 'out-of-state' and then return to Louisiana without any fear of prosecution. She would be required to file a tax return in the State where she worked for her egg donor income. However, that same donor could not be paid for any donation she made within the jurisdiction, even if the payment could be directed to an 'out-of-state' bank. A national egg bank, based outside the restrictive jurisdiction, can recruit, counsel, screen, retrieve and then legally compensate egg donors. Those eggs can then go to a restrictive State after vitrification and proper packaging in liquid nitrogen. In this setting, neither the clinic nor the egg recipient will directly pay a donor for her eggs. Instead the transaction takes place between the clinic/recipient and the egg bank, where the egg bank does not have the status as an 'egg donor'.

29. a) F b) T c) F d) T e) F

Though bilateral tubal patency is not a contra-indication for IUI it is not an absolute requirement for consideration of IUI. This is possibly because the remaining healthy tube may be able to pick up the ovum even if the ovulation happens in the contra-lateral side. IUI will be considered and offered if at least one fallopian tube patency has been established by tests such as HSG, HyCoSy or Laparoscopy. Regular ovulation is a requisite only in natural cycle IUI. However, the current evidence suggests that outcomes are better with stimulated cycle IUI, which offsets the effects of ovulation disorders. Though there is no accepted definition of mild male factor sub fertility, it is acceptable to offer IUI for this indication. This would mean there would be a variation in the sperm counts at different centres. Though there is no absolute quantification of sperm count for mild male factor sub fertility, BFS practise statement suggests that motility is an important determining factor for success with IUI and sets the cut off of 5 million motile sperm for IUI.

30. a) T b) T c) F d) T e) F

The currently published data from HFEA suggests a slightly better livebirth rate at 13% for stimulated cycles vs. 11% for unstimulated DIUI cycles. The multiple pregnancy rate is similar for both the groups - IUI and DIUI. Though one of the commonly perceived reasons for multiple pregnancies was IUI, it was not the case in the recently published data from HFEA. In 2016, the multiple pregnancy rates were 8%. It is likely that the higher proportion of patients having multiple pregnancies after IUI is from outside Europe. The current livebirth rate per cycle for IUI is 12%. The highest birth rates were in patients under 38 years of age (14% for under 35s, and 12% for patients aged 35–37). The rates of successful treatments reduce for patients over 42 years of age.