Laser Assisted Hatching for In-Vitro Fertilisation (IVF)
Executive Summary

[Adapted from the report by ROS AZIAH MOHD RASHID]

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Background

The clinical definition of infertility used by the World Health Organization (WHO) is ‘‘a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse’’. Primary infertility is infertility in a couple who have never had a child while secondary infertility is a failure to conceive following a previous pregnancy.

According to a systematic analysis of 227 national health surveys, approximately 10.5% of women around the world experienced secondary infertility, and roughly 2% experienced primary infertility.

In-vitro fertilisation (IVF) is a type of assisted reproductive technology used for infertility treatment. It is a process of fertilisation where an egg is combined with sperm outside the body. There exist two types of IVF depending on the method used for egg insemination; conventional IVF and IVF with Intracytoplasmic sperm injection (ICSI). Generally, IVF may be used to overcome female infertility when it is due to problems with the fallopian tubes and ICSI can assist in male infertility, such as in those cases where there is a defect in sperm quality (where a sperm cell is injected directly into the egg cell).

The zona pellucida is the hard protein coat surrounding and protecting the genetic material carried within the egg. This layer is approximately 15-20 um thick and must be breached in order for the sperm to make contact with the egg. To establish a successful pregnancy, the developing embryo must break out of its shell (zona pellucida) by a process known as hatching. Once the embryo is hatched, it may implant on the endometrium and begin to grow but if it is unable to hatch, the pregnancy will not continue.

Assisted hatching involves artificial disruption of the zona pellucida using mechanical, chemical or laser. Various AH techniques have been employed including zona thinning, zona drilling (breaching by forming a hole) and complete removal of the zona. American Society for Reproductive Medicine (ASRM) review committee did not recommend routine use of AH during IVF. However, it is used in fertility clinics on patients with poor prognosis such as repeated implantation failures, advanced maternal age, poor quality embryos, and frozen-thawed/ cryopreserved-thawed/ vitrified-thawed embryos.

Laser technology has been used since 1980s in assisted reproductive therapy (ART) techniques such as assisted hatching, embryo biopsy, preimplantation genetic testing, sperm manipulation and etc. As for laser assisted hatching (LAH), it represent as an advancement of ART in enhancing procedural efficiency, reducing the exposure time of gametes and embryos to suboptimal conditions outside the incubator. It also has higher efficacy on pregnancy outcome compared to chemical assisted hatching.

In Malaysia, LAH is only offered in private fertility centre. Therefore, this technology review was requested by Senior Consultant Obstetrics & Gynaecology (reproductive medicine) from Hospital Sultanah Bahiyah in view of introducing/using the technology to increase the pregnancy outcome among IVF patients.

Objective/aim

The objective of this technology review was to evaluate the effectiveness, cost-implication, safety and organisational issues that related to laser assisted hatching for IVF

Results and conclusions
A total of 3512 records were identified through the Ovid interface and PubMed, and 13 were identified from other sources (references of retrieved articles). After removal of 524 duplicates, 3001 records were screened and 2934 were excluded. Of these, 67 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 67 full text articles, 15 full text articles were included and 52 full text articles were excluded. The articles were excluded due to irrelevant study design (n=17), irrelevant population (n=14), irrelevant outcome (n=21). The effectiveness of the included studies is as shown in Table 1.

There was fair to good level of evidenve retrieved to suggests that LAH was associated with slight increased in clinical pregnancy and implantation rate in cryopreserved/frozen-thawed embryo but not for fresh embryo except for study conducted in patient with endometriosis.

Those undergoing LAH were found to have significantly higher multiple pregnancy. On the other hand, there was no significant difference for live birth and miscarriage.

In terms of safety, there was no significant different for minor and major adverse events reported for LAH compared to control. There was no evidence retrieved on the cost-effectiveness and organisational issues of LAH among IVF patients.

Methods
Electronic databases were searched through the Ovid interface: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials - May 2019, EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to May 2019, EBM Reviews - Health Technology Assessment – 2nd Quarter 2019, EBM Reviews – NHS Economic Evaluation Database 2nd Quarter 2019. Searches were also run in PubMed database and U.S. Food and Drug Administration (USFDA) website. Google and Google Scholar was also used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 31st May 2019.

Table 1: Pertinent details of included studies

Author	Study design	Conception method	Sample type	Other	Clinical pregnancy			Implantation rate			Live birth			Multiple pregnancy			Miscarriage		
					LAH	No LAH	P value	LAH	No LAH	P value	LAH	No LAH	P value	LAH	No LAH	P value	LAH	No LAH	P value
Zeng 2018	SR	IVF/ICSI/both	Cryopreserved-thawed	-	OR=1.65 (95%CI:1.24,2.19)		<0.05	OR=1.59 (95%CI:1.06,2.38)		<0.05	OR=1.09 (95%CI:0.77,1.54)		>0.05	OR=2.30 (95%CI:1.30,4.07)		<0.05	OR=0.86 (95%CI:0.50,1.48)		>0.05
Elhanas 2017	RCT	IVF	Frozen	Overall	30/80 (37.5%)	22/80 (27.5%)	0.237	50.00%	47.30%	0.87									
				<35 years	26/56 (46.4%)	16/55 (29.1%)	0.078												
				≥35 years	4/24 (16.7%)	6/25 (24.0%)	0.725												
Lu X 2019	Retrospective cohort	IVF	Frozen	-	111/225 (49.3%)	74/116 (38.9%)	0.034	31.20%	16.95%	0.028	44.80%	35.80%	0.097	32.40%	31.00%	0.847	7.20%	5.40%	0.626
Zhou 2014	Retrospective cohort	IVF	Cryopreserved/ frozen	-	53.96%	33.43%	<0.001	31.85%	16.95%	<0.001	77.04%	70.92%	>0.05				10.81%	25.00%	<0.001
Nada 2018	RCT	ICSI with endometriosis	Fresh	-	46/158 (29.11%)	28/150 (18.67%)	0.002	17.40%	10.20%	0.002	25.32%	16.67%	0.043						
Shi 2016	RCT	IVF	Fresh	overall	40/82 (48.78%)	57/96 (59.38%)	0.157	32.45%	39.29%	0.204							15.85%	15.63%	0.967
				≥35 to 38	29/52 (55.77%)	42/54 (65.63%)	0.279												
				≥38 to 40	8/20 (40%)	11/27 (40.74%)	0.959												
				≥40	3/10 (30%)	4/5 (80%)	0.119												
Horng 2002	RCT	IVF/ICSI	Fresh	≥37 years	7/40 (17.5%)	13/82 (16.3%)	0.864	6.70%	7.30%	0.648									
Tannus 2018	Retrospective cohort	IVF/ICSI	Fresh	-	9.16%	18.44%	0.012				5.37%	12.85%	<0.01						
Li D 2016	SR	-	Mixed fresh/frozen	-	OR=1.03 (95%CI:0.81,1.30)		not mentioned				OR=1.19 (95%CI:0.77,1.83)		not mentioned	OR=1.87 (95%CI:1.33,2.63)		not mentioned	OR=1.03 (95%CI:0.56,1.90)		not mentioned
Elhusiney 2013	RCT	ICSI	Mixed Fresh/frozen	overall	35.10%	28.20%	0.324	33.30%	50.00%	0.23									
				<35 years	18.80%	29.50%	0.159												
				≥35 years	70%	25%	0.001												
				frozen	62.50%	56.30%	0.086												
				fresh	29.50%	21.70%	0.264												
				prevoius 1 trial	68.80%	30.80%	0.04												
Carney 2012	SR	IVF/ICSI	unknown	-	OR=1.04 (95%CI:0.90,1.19)		0.63				OR=1.01 (95%CI:0.81,1.26)		0.95	OR=1.27 (95%CI:1.00,1.61)		0.053	OR=0.98 (95%CI:0.59,1.63)		0.95
Ali J et al. 2003	RCT	ICSI	unknown	≤ 36 years	64.90%	33.30%	0.023	38.10%	17.50%	0.0039									
				≥37 years	15.00%	20.00%	1.00	6.90%	9.30%	0.911									
Antinori 1996	RCT	IVF	unknown	Repeated failure	41/96 (42.7%)	24/104 (23.1%)	<0.05	12.20%	7.30%	<0.05									
				First time	44/111 (39.6%)	23/121 (19%)	<0.05	11.80%	7.10%	<0.05									
Ghannadi 2011	N-RCT	IVF/ICSI	unknown	>35 years	27.71%	16.37%	<0.05							13.04%	5.26%	>0.05			
				≤35 years	50%	30.69%	<0.05							22.27%	5.94%	<0.05			