

## 创新团队成果专栏

## 冰冻胚胎移植子代幼儿的体格和神经认知发育评估

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**[摘要]** **目的**·评估冰冻胚胎移植 (frozen embryo transfer, FET) 子代幼儿的体格和神经认知发育情况。**方法**·招募 248 例经 FET 和自然受孕 (natural conception, NC) 的单胎子代幼儿 (1.5 ~ 4 岁) 作为 FET 子代随访队列, 随访并评估幼儿的体格及神经认知发育。利用多元 Logistic 回归分析评估 FET 子代认知迟缓的潜在风险。**结果**·FET 组与 NC 对照组幼儿的身高、体质量和体质指数 Z 评分构成比间差异无统计学意义。多元 Logistic 回归分析显示, 与 NC 对照组相比, FET 组幼儿的神经认知发育异常和迟缓的风险较高, 尤其在精细运动 ( $OR=3.01$ ,  $95\%CI$  1.48 ~ 6.11) 和社交能力发育方面 ( $OR=3.76$ ,  $95\%CI$  1.63 ~ 8.69); 且在 FET 组中, 女童的社交能力发育风险高于男童。**结论**·FET 对子代幼儿早期的神经认知发育可能有不良影响。

**[关键词]** 冰冻胚胎移植; 体外受精; 体格发育; 神经认知发育

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## Evaluation of physical and neurocognitive development of infants conceived from frozen embryo transfer

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**[Abstract]** **Objective**·To evaluate the physical and neurocognitive development of infants conceived from frozen embryo transfer (FET). **Methods**·Two hundred and forty-eight infants (1.5–4 years old) conceived from FET and natural conception (NC) were recruited as the follow-up cohort of FET offspring, and their physical and neurocognitive development were followed up and evaluated. Multiple Logistic regression analysis was used to assess the potential risk of cognitive retardation in FET offspring. **Results**·There was no significant difference in composition ratio of Z score for height, weight and body mass index between the FET group and the NC control group. Multiple Logistic regression analysis showed that compared with the NC control group, the risk of neurocognitive development abnormalities and retardation was higher in the FET group, especially in fine motor ( $OR=3.01$ ,  $95\%CI$  1.48–6.11) and social development domains ( $OR=3.76$ ,  $95\%CI$  1.63–8.69); and in the FET group, the social development risk of female infants was higher than that of male infants. **Conclusion**·FET may exert a negative impact on the early neurocognitive development of infants.

**[Key words]** frozen embryo transfer (FET); *in vitro* fertilization (IVF); physical growth; neurocognitive development

冰冻胚胎移植 (frozen embryo transfer, FET) 是一项在体外冷冻和保存胚胎, 待解冻后再移植回子宫的技术。自 1983 年第一例 FET 妊娠出现以来<sup>[1]</sup>, 由于其能显著提高累计妊娠率, 减少多胎妊娠和卵巢过度刺激综合征的发生<sup>[2]</sup>, 且伴随着选择性单胚胎移植技术的迅速发展, 其已成为了一种重要的辅助生殖技术 (assisted reproductive technology, ART)。目前, 全世界已有 800 多万名新生儿

通过 ART 诞生<sup>[3]</sup>。欧洲人类生殖与胚胎协会报道, 2015 年 FET 周期数目占 ART 周期总数的 25.7%, 并且持续上升<sup>[4-5]</sup>。多项 meta 分析<sup>[6-7]</sup> 显示, FET 与大于胎龄儿 (large for gestational age, LGA)、妊娠期高血压的风险增加显著相关。一项基于丹麦人群的大型队列研究<sup>[8]</sup> 提示, 与自然受孕 (natural conception, NC) 诞生的子代相比, 经 FET 技术诞生的子代在儿童期的癌症风险有显著增加

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( $HR=2.43$ ,  $95\%CI$  1.44 ~ 4.11)。目前关于 FET 子代的远期健康和发育的报道相对较少<sup>[9]</sup>, FET 对幼儿的潜在生长发育影响亦尚待评估。

幼儿的神经认知发育受到许多出生前事件和环境因素的影响<sup>[10]</sup>。出生后到学龄前期是人类神经系统发育的高峰期,发育迟缓或落后在幼儿时期即可出现,会显著影响子代的生活质量,并对后续发育和智力产生损害。已有调查<sup>[11]</sup>显示,全球约有 2.5 亿小于 5 岁的幼儿存在智力 and 行为等发育异常或发育不良的风险。目前,就 FET 子代的心理、神经发育方面的研究较少,且存在方法学、研究对象异质性等多方面的局限<sup>[3,12]</sup>。值得注意的是,在 FET 子代中 LGA 发生率增加,且子代 LGA 在学龄期发生超重和肥胖的比例显著增高<sup>[13]</sup>,这可能与接受 FET 的妇女在孕期更易发生胎盘功能障碍有关<sup>[14]</sup>。多项研究<sup>[15-17]</sup>提示从儿童到成年期,肥胖和胰岛素抵抗代谢紊乱对认知行为功能存在不良影响。一项西班牙的小样本队列研究<sup>[3]</sup>提示,FET 与其子代 3 岁以下的语言发育迟缓有关。综上,FET 对子代体格、代谢和认知可能存在潜在的不良影响且不容忽视。基于此,本研究测量 FET 子代的体格发育,并使用格塞尔婴幼儿发展量表(Gesell Developmental Schedule, GDS)中文版对 FET 子代的适应性、语言、社交等多方面神经认知及行为发育进行评估。鉴于早期干预可以使发育边缘和轻度落后的幼儿恢复良好<sup>[18]</sup>,本研究纳入对象均为幼儿(4 岁以下),以探索可能的早期筛查和干预时机。

## 1 对象与方法

### 1.1 研究对象

本研究为双向队列研究。根据接受 ART 治疗父母的回顾性信息,于 2018 年 9 月—2019 年 11 月在上海交通大学医学院附属国际和平妇幼保健院招募已接受 FET 以及 NC 出生的幼儿 248 名进行研究并随访。纳入标准:①单胎,妊娠 $\geq 28$  周。②1.5 ~ 4 岁。③定期到医院儿保科参加常规体检。排除标准:①母亲有严重的肝肾功能障碍、糖尿病、癌症或自身免疫系统疾病史。②妊娠前父母至少有一方的体质指数(body mass index, BMI) $>40$ <sup>[19]</sup>。③出生时诊断为严重的先天性畸形<sup>[20]</sup>,染色体异常或先天代谢性疾病。④心脏或神经系统感染疾病。

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### 1.2 方法

**1.2.1 体外受精胚胎移植** 基于母亲的年龄、不孕症的诊断和外周血中窦卵泡个数和抗苗勒激素的浓度水平选择促排卵方案。控制性促排卵(controlled ovarian stimulation, COS)方案包括标准长方案、短方案、拮抗剂等传统方案,以及微刺激方案、个体化联合方案等个体化治疗的新方案<sup>[21-24]</sup>。人绒毛膜促性腺激素(human chorionic gonadotropin, HCG)注射后 34 ~ 36 h 取卵。使用体外受精或卵细胞质内单精子注射(intra cytoplasmic sperm injection, ICSI)的常规方法使卵母细胞受精<sup>[2]</sup>。正常受精卵在培养基中培养至卵裂期(第 2 日或第 3 日)或囊胚期(第 5 日或第 6 日)后进行冷冻<sup>[25]</sup>,胚胎在雌二醇水平和子宫内膜厚度适宜的当天解冻,并进行移植。

**1.2.2 神经认知及行为发育评估** 幼儿的神经行为发育为主要结局。FET 组和 NC 对照组的神经认知及行为发育水平通过国际统一的 GDS 中文版<sup>[26]</sup>进行评估。GDS 为经典的学龄前儿童神经行为发育评估量表,常用于评估幼儿的神经认知及行为发育<sup>[27-28]</sup>。结果以神经运动/认知能区 5 个方面的发育商(development quotient, DQ)得分来表示,包括粗大运动、精细运动、适应性行为、语言、社交能力。以正常行为模式为标准,鉴定观察到的行为模式,DQ 计算公式:[检测到的年龄(月)/实际年龄(月)] $\times 100$ 。DQ 得分 $\geq 85$  分为正常发育,75 ~ 84 分表示可疑神经认知发育迟缓或发育边缘, $<75$  表示发育迟缓<sup>[27]</sup>。

**1.2.3 体格测评** 幼儿体格发育为次要结局。由经过培训的专业医师按照 WHO 的操作规范,对随访幼儿进行体检,测量幼儿的身高及体质量。依据 WHO 发布的幼儿生长发育曲线参考值及评价标准<sup>[27]</sup>,采用 Anthro3.2.2 软件计算相应体格 Z 评分。幼儿的体格 Z 评分=(实测值-参考值中位数)/标准差,包括年龄别身高/身长(H/LAZ)、年龄别体质量(WAZ)、身高/身长别体质量(WH/LZ)、年龄别体质量指数(BMIZ)。进一步将各变量的 Z 评分转化为有临床意义的分类变量,来反映幼儿体格生长发育的不同水平。H/LAZ $<-2$  定义为矮小,WAZ $<-2$  定义为消瘦(包括严重消瘦)。WHZ/BMIZ $<-2$  为营养不良,-2 ~ 2 为正常, $>2$  为超重和肥胖<sup>[29]</sup>。

**1.2.4 信息采集** 与幼儿的神经行为发育结局相关的协变量较多,持续存在于母亲孕前到子代的幼儿阶段,如父母年龄<sup>[30]</sup>、子代早产和低出生体质量<sup>[31]</sup>、母亲妊娠亚甲状腺功能紊乱<sup>[32]</sup>、父母吸烟<sup>[33]</sup>、幼儿营养和微量元素补充<sup>[34]</sup>、乙肝<sup>[27,35-36]</sup>、母亲孕期环境污染及有害粉尘暴露<sup>[37]</sup>、母乳喂养<sup>[38-39]</sup>。通过电子问卷采集母亲孕育史、孕期信息、出生结

局和父母家庭环境等社会人口学信息。通过病例资料收集父母既往史, 孕前到出生以及体外受精治疗的相关信息。

1.3 统计学方法

采用 SPSS 25.0 软件对研究数据进行统计分析。研究对象的基线信息及幼儿发育结局资料中, 符合正态分布的定量资料以  $\bar{x} \pm s$  表示, 采用  $t$  检验进行分析; 不符合正态分布的定量资料以  $M(Q_1, Q_3)$  表示, 采用 Mann-Whitney  $U$  检验进行分析。定性资料以频数和百分率表示, 采用  $\chi^2$  检验或 Fisher 精确检验进行分析。采用向前似然比检验 (forward-likelihood ratio, forward-LRT) 筛选变

量, 得到优化后的多元 Logistic 回归模型, 评估 FET 对子代幼儿神经认知发育的影响。 $P < 0.05$  表示差异有统计学意义。

2 结果

2.1 基线特征

研究队列的基线特征见表 1, 在 248 例幼儿中, FET 组 182 例, NC 对照组 66 例。2 组男女比例近似 1:1, 其出生体质量和孕周间差异均无统计学意义, 但 FET 组 LGA 和巨大儿的比例更高 ( $P=0.028$ ,  $P=0.009$ )。

表 1 FET 组和 NC 对照组幼儿及父母的基线特征  
Tab 1 Baseline characteristics of infants and their parents in the FET group and the NC control group

Item	NC control group (N=66)	FET group (N=182)	$t/z/\chi^2$	P value
Father				
Age/year <sup>①</sup>	32.02 ± 4.01	34.23 ± 4.01	-3.47	0.001
BMI/ (kg · m <sup>-2</sup> )	23.97 ± 3.16	24.53 ± 3.72	-1.07	0.286
Smoking/n (%)	21 (31.8)	68 (37.4)	0.65	0.421
Mother				
Age at pregnancy/year <sup>②</sup>	30.0 (28.0, 34.0)	32.5 (29.0, 35.0)	-2.90	0.004
BMI/ (kg · m <sup>-2</sup> ) <sup>③</sup>	21.05 ± 2.80	22.09 ± 3.41	-2.22	0.028
Smoking/n (%) <sup>④⑤</sup>	0 (0)	3 (1.6)	—	0.567
Duration of breastfeeding/month <sup>②</sup>	8.0 (6.0, 12.0)	7.0 (3.0, 12.0)	-1.89	0.059
PIH/n (%)			1.89	0.345
hypertension (only)	1 (1.5)	12 (6.7)		
preeclampsia	1 (1.5)	4 (2.1)		
Multipara /n (%)	17 (25.8)	14 (7.7)	14.45	0.000
Children				
Male/n (%)	38 (57.6)	96 (52.7)	0.455	0.500
Age/month <sup>②</sup>	36.4 (32.1, 41.2)	32.6 (26.1, 35.23)	-5.02	0.000
Birth outcome				
Birth weight/g <sup>②</sup>	3 407.5 (3 197.5, 3 655.0)	3 415.0 (3 042.5, 3 727.5)	0.42	0.673
Gestational time/week <sup>②</sup>	38.0 (38.5, 39.0)	39.0 (38.0, 39.0)	-0.67	0.502
PTB/n (%)	4 (6.1)	21 (11.5)	1.60	0.205
LB (<2 500 g) /n (%) <sup>⑥</sup>	1 (1.5)	12 (6.6)	—	0.194
Macrosomia (>4 000 g) /n (%)	1 (1.5)	23 (12.6)	6.86	0.009
LGA/n (%)	4 (6.1)	31 (17.0)	4.81	0.028
SGA/n (%) <sup>⑥</sup>	1 (1.5)	12 (6.6)	—	0.194
Early education/n (%)	51 (77.3)	106 (58.2)	7.55	0.006

**Note:** PIH—pregnancy induced hypertension; PTB—preterm birth; LB—low birth weight; SGA—small for gestational age. <sup>①</sup> For NC control group: paternal age when the women was pregnant; for FET group: age at sperm supply. <sup>②</sup> Non-parametric test, Mann-Whitney  $U$  test. <sup>③</sup> From one year before conception to labor. <sup>④</sup> Fisher exact test.

2.2 认知和体格发育水平

结果 (表 2、表 3) 显示, 2 组幼儿的各项 Z 评分构成比间差异均无统计学意义, 提示体格发育水平相似; 而 2 组在认知结局方面特别是 FET 组中女性子代在精细运动

和社交能力的发育水平与 NC 组相比, 差异均具有统计学意义 ( $P=0.003$ ,  $P=0.026$ )。此外, 女性子代群体中, 仅 FET 组出现粗大运动、适应性行为、语言、社交能力的发育迟缓, 分别占比为 4.7%、1.2%、3.4% 和 9.3%。

表 2 2 组幼儿体格发育的比较  
Tab 2 Comparison of physical development between the two groups

Physical development	NC control group (N=66)	FET group (N=182)	$\chi^2$	P value
H/LAZ/n (%)				
Stunted (<-2)	0 (0)	2 (1.1)	—	1.000
WAZ/n (%)				
Underweight (<-2)	0 (0)	1 (0.5)	—	1.000
WH/LZ/n (%)				
Wasted (<-2)	0 (0)	1 (0.5)	1.986	0.449
OWO (>2)	2 (3.0)	14 (7.7)		
BMIZ/n (%)				
Wasted (<-2)	0 (0)	2 (1.1)	2.659	0.226
OWO (>2)	2 (3.0)	16 (8.8)		

Note: OWO—overweight and obese. Fisher exact test was used as the statistical test.

表 3 2 组幼儿神经认知和行为发育比较  
Tab 3 Comparison of neurocognitive and behavioral development between the two groups

Neurocognitive development	Male				Female			
	NC control group (N=38)	FET group (N=96)	$\chi^2$	P value	NC control group (N=28)	FET group (N=86)	$\chi^2$	P value
Gross motor/n (%)			0.433	1.000			1.665	0.484
≥ 85	36 (94.7)	91 (94.8)			26 (92.9)	79 (91.9)		
75 ~ 84	1 (2.6)	2 (2.1)			2 (7.1)	3 (3.5)		
<75	1 (2.6)	3 (3.1)			0 (0)	4 (4.7)		
Fine motor/ n (%)			0.746	0.804 <sup>①</sup>			12.362	0.003 <sup>①</sup>
≥ 85	21 (55.3)	57 (59.4)			23 (82.1)	47 (54.7)		
75 ~ 84	12 (31.6)	30 (31.3)			1 (3.6)	27 (31.3)		
<75	5 (13.2)	9 (9.4)			4 (14.3)	12 (14.0)		
Adaptability/ n (%)			1.003	0.805			0.847	1.000
≥ 85	37 (97.4)	91 (94.8)			28 (100.0)	84 (97.6)		
75 ~ 84	1 (2.6)	2 (2.1)			0 (0)	1 (1.2)		
<75	0 (0)	3 (3.1)			0 (0)	1 (1.2)		
Language/ n (%)			1.463	0.550			1.346	0.497
≥ 85	32 (84.2)	86 (89.6)			28 (100.0)	79 (91.9)		
75 ~ 84	4 (10.5)	5 (5.2)			0 (0)	4 (4.7)		
<75	2 (5.3)	5 (5.2)			0 (0)	3 (3.4)		
Sociability/ n (%)			2.307	0.355 <sup>①</sup>			7.483	0.026 <sup>①</sup>
≥ 85	30 (78.9)	64 (66.7)			27 (96.4)	67 (77.9)		
75 ~ 84	5 (13.2)	19 (19.8)			1 (3.6)	12 (12.8)		
<75	3 (7.9)	13 (13.5)			0 (0)	7 (9.3)		

Note: <sup>①</sup>  $\chi^2$  test. Others were Fisher exact test.



2.3 FET 组子代早期的认知发育不良风险

通过多元 Logistic 逐步回归分析调整协变量并优化, 结果见表 4。FET 组幼儿的精细运动和社交能力均存在显著增加其发育异常和迟缓的风险 (均  $P=0.002$ ); 当对性

别进行单独评估时, 结果显示 FET 女性子代的精细运动以及男女的社交能力发育均存在显著增加其发育不良或发育迟缓的风险 (均  $P<0.05$ ), 且女性比男性的相对风险更高。

表 4 亚组中 FET 对子代幼儿神经认知发育异常和迟缓的影响的多元 Logistic 回归分析  
Tab 4 Effects of FET on neurocognitive development abnormality and retardation of offspring in the subgroups by multiple Logistic regression analysis

	Fine motor (DQ<85 score)		Sociability (DQ<85 score)	
	OR (95%CI)	P value	OR (95%CI)	P value
All children	3.01 (1.48—6.11)	0.002 <sup>①</sup>	3.76 (1.63—8.69)	0.002 <sup>②</sup>
Male children	1.72 (0.69—4.32)	0.245 <sup>①</sup>	2.83 (1.07—7.51)	0.036 <sup>③</sup>
Female children	6.90 (2.04—23.3)	0.002 <sup>①</sup>	9.27 (1.14—75.24)	0.037 <sup>③</sup>

Note: <sup>①</sup> Adjusted for age and age at pregnancy. <sup>②</sup> Adjusted for age and gender. <sup>③</sup> Adjusted for age.

3 讨论

本研究对 2 组幼儿的神经认知发育进行比较, 结果显示其主要发育水平间差异具有统计学意义, 特别是子代女性的精细运动和社交能力方面 ( $P=0.003$ ,  $P=0.026$ )。多元 Logistic 回归分析验证了 FET 对子代女性的不良影响; 此外, FET 对子代男性的社交发育的不良影响也有统计学意义, 但比女孩相对低。英国的一项研究<sup>[40]</sup>招募了 91 名经 FET 诞生的幼儿和 83 名 NC 诞生的幼儿, 2 组在幼儿期的神经行为和认知发育水平间差异无统计学意义, 但玻璃化冷冻胚胎合并先天畸形的神经运动评分较低。另一项瑞典的研究<sup>[41]</sup>随访了 FET、NC 和新鲜胚胎移植诞生的子代, 神经发育紊乱性疾病仅出现在 FET 组中, 患病人数为 3 (1.2%)。另有研究<sup>[3]</sup>提示, FET 与子代 3 岁以下婴幼儿的语言发育迟缓相关, 语言与社交能力相互影响, 可能根据幼儿特征先后出现。这与我们的研究结果类似, 提示 FET 本身或过程中或存在与社交能力发育独立相关的风险因素, 可能的中间机制之一即是 FET 增加了巨大儿、LGA、妊娠高血压、子痫、胎盘血管病变异常的风险<sup>[6-7, 42]</sup>。已有研究<sup>[43]</sup>提示先兆子痫与子代智力异常高度相关, 且从本研究结果可见 FET 组孕期妊娠高血压 / 子痫前期的比例均高于 NC 对照组。此外, 一项队列研究<sup>[44]</sup>提示, 与传统体外受精新鲜胚胎移植组相比, 冰冻胚胎移植卵胞浆内单精子显微注射 (intracytoplasmic sperm injection, ICSI) 组与新鲜胚胎移植 ICSI 组子代的神经认知发育迟缓风险均显著增高, 冰冻胚胎移植 ICSI 组的风险明显更高, 因此 FET 特有的冻融程序或可对子代精神和认知发

育存在不良影响, 特别是 ICSI 因素存在的情况下, 可能与其产生了交互作用。

在分子机制和遗传水平上, 认知发育风险增加可能的原因之一是与 ART 相关体外操作通过改变基因印记或表观遗传对后期胚胎及子代发育产生影响<sup>[42, 45-46]</sup>。研究<sup>[47]</sup>表明, 体外受精可以改变新生儿血液中特定基因组的甲基化, 而新生儿的基因组甲基化处于亚稳态状态, 因此对某些表观基因组将存在持久的影响。大量的动物实验表明, 胚胎植入前的体外培养和操作<sup>[48-50]</sup>、FET 冻融程序<sup>[51]</sup>与子代的远期生长发育、神经行为受损、体质量、代谢紊乱风险相关, 而这些不利因素都可能影响 FET 子代的神经认知和生长发育。此外, Sun 等<sup>[52]</sup>的研究表明, 人类卵裂球胚胎解冻后再培养一段时间, 可发现明显增高的多核发生率, 且远高于新鲜胚胎移植。Seikkula 等<sup>[53]</sup>的病例对照研究则纳入多核或双核冰冻胚胎移植周期的妇女和子代作为病例组, 病例组的临床妊娠率和活产率与正常组相比都显著降低, 提示 FET 组的多核胚胎发生对后续胚胎发育和子代发育具有潜在的不良影响。

子代早期的认知发育对后期成长有很大影响<sup>[54]</sup>, 大脑在婴幼儿时期具有很强的可塑性, 对神经认知发育轻度迟缓或边缘状态的幼儿进行积极的早期干预, 可能将获得较理想的效果<sup>[18]</sup>。因此, 建议在发育早期即婴幼儿时期, 密切关注 FET 子代的社交行为以及子代女性的精细运动等神经认知发育情况, 必要时进行早期筛查和干预。有研究<sup>[38]</sup>表明延长母乳喂养对幼儿的认知行为发育是一个独立保护因素, 而接受 ART 的母亲的母乳喂养水平普遍低下<sup>[55]</sup>, 因此促进母乳喂养或可帮助子代幼儿改善、恢复和

实现追赶生长。

本研究结果显示, FET组与NC组的子代在小于4岁的幼儿时期, 其体格发育水平相似, 但FET子代在精细运动和社交能力发育迟缓的风险增加; 虽然在多元Logistic回归分析时校正了幼儿早教这一潜在混杂因素,

但并不能排除父母过度保护、育儿意识欠缺的混杂以及家庭的潜在选择偏倚。由于本研究样本量较小, 可能存在一定的局限性和偏倚, 鉴于幼儿时期认知发育对生活质量和后续认知发育的持续影响, 将来可增加样本量并延长随访时间, 对上述研究结果做进一步的验证。

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## “双一流”暨高水平地方高校建设项目

### 一流学科——药学

瞄准药学科学前沿和经济社会发展对重大疾病创新药物、食品药品安全的迫切需求,以科研创新和成果转化为重点,提升跨学科、跨行业的协同创新能力和知识服务能力;加强高端人才引进培养和学科结构的优化,建设国际领先的药物设计和结构生物学、高内涵药物筛选、药物动力学和药物代谢组学、药物毒理学和转化毒理学等技术平台,以及符合国际规范的临床试验基地;关注药理学、临床药理学和毒理学等重点研究方向;争取成为具有明显特色和一定国际影响的学科,药学一级学科点跻身国内学科排名前10%。







## 特约创新团队介绍

### 创新团队名称

生殖医学战略创新团队

### 团队主要成员

### 团队负责人介绍

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致力于研究生殖内分泌疾病及助孕安全, 在国际上首次提出“配子源性疾病”理论学说, 对精/卵源性疾病的代间及跨代遗传/表观遗传机制进行了开创性研究, 聚焦辅助生殖技术 (assisted reproductive technology, ART) 出生子代近远期健康的关键科学问题, 通过 ART 出生队列和基础研究, 创建生殖新技术, 源头阻断遗传性出生缺陷, 提高了试管婴儿的安全性。作为第一完成人获国家科技进步奖二等奖、全国妇幼健康科学技术奖一等奖, 获“全国三八红旗手”“白求恩式好医生”“卫生部有突出贡献中青年专家”等荣誉称号。主编多部著作, 担任 *Endocrinology* 和 *Fertil & Steril* 等 7 个 SCI 期刊编委。

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Dr. HUANG specialized in reproductive endocrine disorders and assisted pregnancy safety, proposed the theory of “gamete and embryo-fetal origins of adult diseases”, and carried out a pioneering study on the intragenerational and intergenerational genetic/epigenetic mechanisms of sperm/egg-derived diseases for the first time. In view of the key scientific issues of the near and long-term health of the children born with assisted reproductive technology (ART), the new reproductive technologies were created through ART birth cohort and basic research to improve the safety of *in vitro* fertilization baby and prevent the hereditary birth defects from the source. She won the second prize of National Science and Technology Advancement Award and the first prize of National Maternal and Child Health Science and Technology Award as the first author. Meanwhile, she won the following honorary titles, including “March Eighth Red Banner Pacesetter” “Bethune Good Doctor” “Young and Middle-aged Experts with Outstanding Contributions Prized by the Ministry of Health”. Moreover, she also compiled many works and served as the editorial board member of 7 SCI journals, including *Endocrinology* and *Fertil & Steril*.



## 主要研究方向

黄荷凤教授团队致力于从生命起源的配子发生、胚胎和胎儿发育阶段探索成人期疾病如糖尿病、心血管病的发生机制，精准防控单基因病、染色体病等遗传性出生缺陷。通过多年的研究，凝练出的胚胎/胎儿源性疾病和遗传性出生缺陷防控这两大研究方向是发育和生殖研究领域的一个新方向；并创新性引入基因编辑等新兴技术，不断完善和优化植入前胚胎诊断技术体系，从源头实现重大疾病和遗传性出生缺陷的早期防治。团队人员在 *Nat Med* 和 *PNAS* 等著名期刊上发表论文共计 260 余篇，他引 3 000 余次，在国际干细胞研究学会会议、美国心脏协会会议、Weinstein 国际心血管会议等学术会议及科研机构报告 50 余次。

Dr. HUANG's team is committed to exploring the occurrence mechanism of adult diseases such as diabetes and cardiovascular diseases from the gametogenesis, embryo and fetal development stages of life origin, and precisely preventing and controlling genetic birth defects such as monogenic diseases and chromosomal diseases, which is a new direction in the field of development and reproduction research. Through years of research, the team has condensed 2 research directions of prevention and control of embryo/fetal diseases and genetic birth defects, explored the mechanism of adverse events in early life inducing chronic diseases in adulthood, innovatively introduced emerging technologies such as gene editing, and continuously improved and optimized the preimplantation embryo diagnosis technology system to realize major diseases and genetic birth defects from the source to achieve the early prevention and control. The team members published more than 260 papers on the famous journals such as *Nat Med* and *PNAS*, cited more than 3 000 times, and reported more than 50 times in academic conferences and research institutions such as International Society for Stem Cell Research (ISSCR) Conference, American Heart Association (AHA) Conference, Weinstein Development Conference, etc.

## 近 2 年代表性成果

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- 9) Chen JY, Zhao XZ, Cui L, et al. Genetic regulatory subnetworks and key regulating genes in rat Hippocampus perturbed by prenatal malnutrition: implications for major brain disorders[J]. *Aging(Albany NY)*, 2020, 12(9): 8434-8458.

