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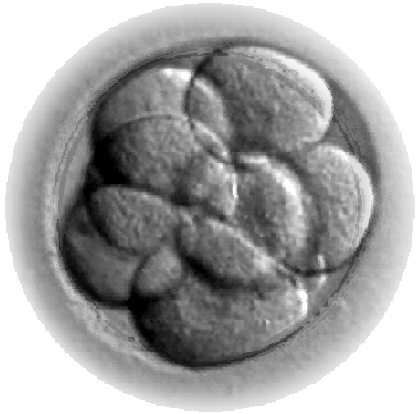

PGD for HLA matching

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Preimplantation HLA matching

- One of the latest applications in reproductive medicine.
- Viable option for couples with children needing haematopoietic stem cell (HSC) transplantation.
- Selection of embryos both free of disease and HLA matched with the existing child.
- PGD is used not only to avoid the birth of affected children, but also to conceive healthy children who may also be potential HLA-identical donors of HSC
- At delivery of the newborn, cord blood HSC can be used to treat the affected sibling.
- A different role for PGD: from diagnosis to treatment

Allogeneic HSC transplantation

- Only curative option for severe cases of haematopoietic disorders.
- A critical factor associated with a favourable outcome is the use of HLA identical donors
- HSC from HLA identical siblings provide the higher success rates
- Reduced incidence of graft rejection and other serious complications associated with transplantation.
- Transplantation using non HLA-identical donors is associated with higher morbidity and poorer survival.
- Limited availability of HLA-matched unrelated donor, identified from national or international registers.

Indications for cord blood transplantation

Indication			Cure (%)
As a rule	Congenital	Thalassemia major	70-90
		Sickle cell anemia	80-90
		Fanconi's anemia	80-90
		Immunodeficiencies	70-90
		Blackfan-Diamond anemia	>50
	Acquired	Severe aplastic anemia	80-90
As an exception	Acquired	Acute lymphoblastic leukemia	30-50
		Chronic myeloid leukemia	40-80
		Non Hodgkin lymphoma	30-50
		Myelodysplastic syndrome	30-50

Indications for HLA typing

Indications	No. of PGD cycles	No. of couples	Clinical pregnancies	Babies born	CBT
HLA typing combined with PGD					
Sickle cell disease	8	4	3	3	2
Beta-thalassemia	215	108	53	45	7
Fanconi anemia	1	1	0	0	1
Wiskott Aldrich' syndrome	1	1	1	1	1
Chronic granulomatous disease	1	1	1	2	0
Duncan syndrome	2	1	1	1	0
Mannosidosis Alpha	2	1	0	0	0
Hurler syndrome	2	2	0	0	0
Gaucher disease	4	1	1	0	0
Bruton agammaglobulinemia	1	1	1	2	0
Glanzmann thrombasthenia	1	1	0	0	0
Adrenoleukodystrophy	3	2	1	1	0
HLA-only typing					
Acute lymphoblastic leukemia	40	29	12	10	2
Diamond Blackfan anemia	17	3	4	2	2
Histiocytosis	3	1	1	1	0
Total	**301**	**157**	**79**	**68**	**15**

Fiorentino *et al.* (2004) Mol Hum Reprod 10: 445-460; Fiorentino *et al.* (2005) Eur.J.Hum Genet. 13: 953-958; Van de velde, Fiorentino et al., (2009) Hum reprod 24, 732–740,

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Clinical results: pregnancies and babies

	HLA+PGD	HLA-only	Total
Maternal age	31.6 ± 4.8	37.3 ± 3.6	32.6 ± 5.1
No. of cycles performed	241	60	301
• per couple	1.8 ± 1.2	2.1 ± 1.7	1.9 ± 1.3
No. of transfers (%)	165 (68.4)	45 (75.0)	210 (69.8)
No. of embryos transferred	253	75	328
Mean no. of embryos transferred	1.0 ± 1.7	1.2 ± 0.9	1.1 ± 0.7
No. of clinical pregnancies	62	17	79
• Clinical per cycle	25.7%	28.3%	26.2%
• Clinical per transfer	37.6%	37.7%	37.6%
Miscarriages	11	4	15
No. of embryos implanted	78	18	96
• Implantation rate	30.8%	24.0%	29.3%
No. of pregnancies went to term	51	13	64
No. of babies born	55	13	68
Live birth rate per cycle	21.2%	21.7%	21.3%

Data modified from: Fiorentino *et al.* (2004) Mol Hum Reprod 10: 445-460; Fiorentino *et al.* (2005) Eur.J.Hum Genet. 13: 953-958 ; Van de velde, Fiorentino et al., (2009) Hum reprod 24, 732–740

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Limitations

- A minimal time period is needed for the procedure: a delay of 12 to 18 month may be necessary between decision making and treatment (mainly related with the success of IVF treatment)
- A high number of embryos (and therefore several IVF cycles) may be necessary to obtain a pregnancy and a live birth.
- The low chance of finding an HLA matched unaffected embryo (18.75%).
- The chance of obtaining a pregnancy in IVF is mainly limited by the advancing age of the mother.

Ponchiroli's family

- The couple has a son affected by a sporadic for of **Blackfan-Diamond anemia**, an extremely rare disease affecting only 600-700 world-wide, characterized by an inability to produce red blood cells.
- The only cure available was HSC transplantation.
- No genetic risk, HLA matching as primary indication.
- 3 years of attempts:
  - ✓ 7 PGD cycles
  - ✓ 2 different IVF centres

Ponchiroli's case clinical results

No. of years of attempts	3 (36-39 y.o.)
No. of cycles performed (2 different centres)	7 (2+5)
No. of oocytes retrieved	152
No. of mature oocytes injected	114
No. of oocytes fertilized	104
No. of embryos analyzed	86
No. of embryos diagnosed (%)	81 (94.2)
HLA identical healthy embryos (%)	15 (18.5)
HLA non-identical embryos (%)	66 (81.5)
No. of embryos transferred (mean)	13 (1.9±1.2)
No. of transfers	6
No. of +HCG pregnancies	3
No. of clinical pregnancies	2
Miscarriages	1
No. of babies born	1
CBT	1

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Ponchiroli's case

- A hard but happy ending story.
- The son is now completely cured after HSC transplantation.
- An example of perseverance, a strong act of love.

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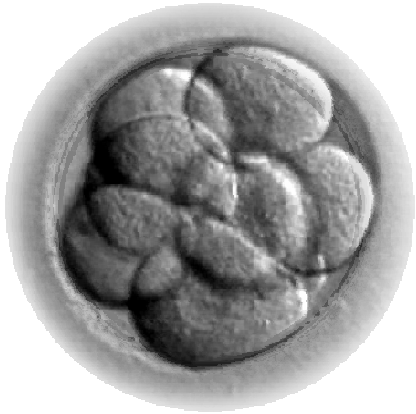

PGD for HLA matching:

how we cured our child following a PGD treatment

Cesare PONCHIROLI