Prenatal genetic counselling: issues and perspectives for pre-conceptional health care in Emilia Romagna (Northern Italy)

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ABSTRACT

BACKGROUND: there are many reasons why a couple may seek specialist genetic counselling about foetal risk. The referral for prenatal genetic counselling of women with a known risk factor during pregnancy has many disadvantages. Despite this, 10-20% of women seek counselling when already pregnant.

METHODS: data on 804 pregnant women out of 2 158 (37.3%) referred for genetic counselling in 2010 to three Clinical Genetic Services were retrospectively analysed. Patients referred only for advanced maternal age were analysed in a separate study.

RESULTS: the 804 pregnant women were referred for 932 counselling issues. 325 issues (34.9%) were identified during pregnancy and 607 (65.1%) were pre-existing. 81.2% of Italians compared to 41.8% of the non-Italians (P<0.01) had access to counselling before 13 weeks of gestation for risk factors present before pregnancy. An accurate genetic diagnosis was available in 25.0% of cases. In 21.7% of the cases an elevated a *priori* risk of >10% for the unborn child was established.

CONCLUSIONS: genetic services provide 37.3% of counselling to pregnant women. Referral for genetic counselling during pregnancy can require considerable resources and pose significant ethical and organizational challenges. New models of pregnancy care in the community need to be developed. General practitioners and gynaecologists have an important role in the referral and in the defence of equity of access and a more structured approach to the participation of medical geneticists to primary practice should be considered.

Key words: Genetic counselling; Referral; Pregnancy; Pre-conceptional care

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DOI: ***10.2427/8870***
Published as Online First on January 22, 2014

INTRODUCTION

Prenatal genetic counselling deals with the determination of risk factors for the foetus. The reasons for seeking genetic counselling by pregnant women for foetal risk determination are extremely varied and can be broadly described as 1) risk factors detected during pregnancy and 2) pre-existing risk.

In the first case, the genetic counselling

is required to assess the risk for the foetus for mental or physical disabilities after detection of morphological or chromosomal abnormalities resulting from prenatal diagnosis. Here an expert opinion is sort to help the couple decide whether to continue the pregnancy or not.

In the second case, referral for familial genetic counselling during pregnancy has important disadvantages compared to pre-conceptional reproductive counselling [1-4]: it may be too late for invasive prenatal diagnosis, the woman may be deprived of the choice to terminate a pregnancy and the preventative and therapeutic options are limited. The alternative reproductive options, like pre-implantation genetic diagnosis or donor insemination conception are not an option and the couples are faced with the psychological stress of making important decisions in a short period of time [5, 6].

Despite these disadvantages, and increasing knowledge about possible risks to the foetus during pregnancy due to parental medical conditions, obstetric and family history and environmental exposure, referral to clinical genetic services takes place to a limited degree or somewhat late [3, 7, 8-14]. Late referrals require considerable resources in order to provide less than optimum solutions for the couple. They pose significant organizational challenges for the development of clinical services and the formulation of public health policy regarding access, equity and funding [15-18]. To our knowledge few studies have addressed this issue recently.

In Emilia Romagna Region (Italy), as in other countries, genetic counselling is restricted to specific genetic counselling centres (www.geneter.it) and women who might benefit from genetic counselling are usually identified by their general practitioner or obstetrician-gynaecologist.

In the present study a series of 804 pregnant women referred in 2010 were analysed. Women referred for age-related risk factors were excluded. The family and personal history from consultation sessions was used to evaluate the type of foetal risk and gain information on alertness towards genetic issues and pregnancy care in the Emilia Romagna Region healthcare referral system.

METHODS

Records of 804 pregnant women referred over a 1-year period (2010) to prenatal genetic counselling in one of three Emilia-Romagna Region Clinical Genetic Services participating in the study (Ferrara, Bologna and Imola) were reviewed. Approval for the study was obtained from the Institutional Review Board of the leading Centre of the study (University of Ferrara).

The Genetic Centres involved serve a defined geographic area (Area Vasta Emilia Centrale) with a population of around 1 350 000 inhabitants and 11 818 births in 2010. These Genetic Centres also provide clinical genetic support and counselling for a variety of other indications (e.g. neuromuscular disorders and dysmorphology) during and outside pregnancy. They are linked for coordination and development to the Regional Genetic Healthcare System. In all three Centres pedigree analysis and counselling are provided by trained medical geneticists. Requests for counselling are dealt with by skilled personnel with a data set of basic identifiers, including referring physicians and referral indication. The data are confirmed at the first consultation and registered in the database of the Centre, in accordance with the Italian Data Protection Laws.

Pregnant women referred with the indication of possible risk for the foetus are usually identified by obstetricians-gynaecologists or more rarely by general practitioners or other specialists.

Of the 2 158 counselling requests in 2010, our retrospective study concentrated on 804 (37.3%) pregnant woman who were referred with the indication of possible risk for the foetus.

Pregnant women referred for age-related risk factors were excluded from this study as they have been reported separately (Pompili et al submitted).

A computer program was created using Microsoft Access to transfer information from the clinical notes and facilitate data analysis.

Three geneticists (G.P., E.P. and M.L.) evaluated:

1. The general characteristics of the pregnant women in the study (age, nationality, previous births and / or abortions)
2. The issues related to genetic counselling (weeks of gestation at the beginning of counselling, reasons for referral)
3. The foetal risk at the end of the consultancy [19].

The characteristics of the reference population were derived from the Emilia

Romagna Certificate of assistance at Birth database (CedAP).

Counselling issues were divided into two groups:

1. *Risk factors detected during pregnancy:* Maternal exposure (medication, radiation, infection) or abnormal results of cytogenetic testing or ultrasound. The study does not include women referred to their gynaecologist to discuss the implications of an adverse outcome after routine prenatal diagnosis. In the Emilia Romagna Region a standardised protocol for these conditions has not been established. Referral to genetic counselling for these issues is not homogeneous but nevertheless represents a significant proportion (34.9%) of genetic counselling during pregnancy. It is an expert opinion to help the couple decide whether to continue the pregnancy or not.
2. *Pre-existing risk.* Consanguinity, known Mendelian conditions, occurrence or recurrence of specific diseases in the family, presence of hereditary predisposition without a defined inheritance pattern or heterogeneous hereditary conditions.

At the beginning of counselling the pregnancy was defined as: first trimester (less than or equal to 13 weeks), 14-18 weeks (period in which amniocentesis is performed), 19-24 weeks (period in which under Italian law termination is legal) and >25 weeks gestation.

Three levels of diagnostic definition at referral were used:

1. *No precise clinical diagnosis defined prior to counselling* (e.g. intellectual disability with no other diagnosis) or genetics test not available (e.g. environmental hazards).
2. *Specific clinical diagnosis with no genetic diagnosis.* A precise clinical diagnosis (e.g. Fragile X Syndrome diagnosed from clinical and family history) with no genetic mutation identified.
3. *Specific clinical and genetic diagnosis.* Cases with a complete clinical and genetic diagnosis (mutation or chromosomal abnormality characterised).

Based on the individual and family history and available clinical and laboratory data the foetal risk of a genetic disease or a serious structural anomaly was considered:

1. **Negative/not significant.** No genetic disorder or birth defects reported or no influence of the history on foetal risk. No laboratory test information of concern (e.g. a father's paternal uncle with an X-linked disease, or an isolated cancer in a second or third degree relative). The risk is equal to that of the general population.
2. **Not determined.** Reliable information not available. Despite a detailed family/personal history and laboratory tests a precise estimation of foetal risk was not possible.
3. **Risk 5-10%.** Possible presence of etiologically heterogeneous heritable disorders (e.g. familiarity for unexplained mental retardation) or a probable multifactorial disorder (e.g. familiarity for an isolated neural tube defect or cleft lip/palate). The magnitude of the risk was identified through empirical survey data.
4. **Risk >10%.** A monogenic or chromosomal hereditary condition present. The magnitude of the risk was derived from pure Mendelian risk or Mendelian risk modified by Bayesian calculations or chromosomal risk derived from published literature or specific databases. No cases of mitochondrial diseases were identified.

Statistical Analysis

The Chi-square test to compare differences was used. The significance level was set at $P<0.05$.

RESULTS

During the study period, 804 eligible pregnant women were referred to genetic counselling.

597 (74.2%) were Italian and 207 (25.8%) non-Italian women in line with the general population for births in the Emilia Romagna Region [20].

The mean maternal age was 32.5 years (SD 5.9) and the mean gestational age at time of counseling was 13.2 weeks (SD 5.55 weeks).

No significant differences were found between cases and the reference population except for the number of previous children (P>0.01). Patients' characteristics are summarized in Table 1.

The 804 pregnant women were referred for 932 counselling issues. Of these issues, 325 (34.9%) were evident during pregnancy (Table 2) and 607 (65.1%) were pre-existing. A significant difference (P<0.01) exists between Italians (37.8%) and non-Italians (26.6%) for counselling issues detected in pregnancy.

The main counselling issues for risk factors detected during pregnancy are maternal exposure 18.5% (172/932) followed by detection of chromosomal abnormalities in the foetus 11.3% (105/932) (Table 2).

The main counselling issues for pre-existing risk factors are the presence of a monogenic condition in one (or both) of the couple or in a first degree relative (43.8%; 408/932), followed by presence of multifactorial/heterogeneous conditions in the couple or in close relatives 12.3% (115/932) (Table 3).

A significant difference (P<0.01) was seen between Italian and non-Italian women for the presence of a monogenic condition in the family: 41.2% for Italians (285/691) compared to 51% for non-Italians (123/241).

65.0% of counselling issues were requested in the first trimester (606/932) with a significant difference (P<0.01) between Italians 72.6% (502/691) and non-Italians 43.2% (104/241).

Access to counselling before 13 weeks of gestation due to the presence of risk factors known before pregnancy was significantly different: 81.2% (349/430) of Italians compared to 41.8% (74/177) of the non-Italians (P<0.01). 11 cases of non-Italian women with family history for genetic conditions came for counselling after 25 weeks of gestation (Table 3).

In 394 (42.3%) cases (273+121) the reason for referral did not allow an immediate risk evaluation but needed further clinical and anamnestic data in order to evaluate the risk. In 305 (32.7%) cases (220+85) the reason for referral allowed a risk evaluation. In 233 (25.0%) (198+35) cases the condition was genetically defined by a known mutation (Table 4 and 5). Again a significant difference was seen (P<0.01) between Italians and non-Italians arriving for counselling with a genetically defined condition; 28.7% of Italians (198/691) compared to 14.5% (35/241) non-Italians (Table 5).

In 564 cases 60.5% (564/932) the final risk for the foetus was estimated not significantly different from that of the general population. 21.7% (153+49/932) of the pregnancies had a risk factor >10% (Table 6).

TABLE 1

PATIENTS CHARACTERISTICS AND COMPARISON WITH REFERENCE POPULATION (2010)

CHARACTERISTICS	%/NO.	REFERENCE POPULATION**
Mean maternal age	32.5 (5.9 SD*)	32.4 (5.4 SD)
NATIONALITY		
Italian	74.2% (597)	76.4% (8 305)
Non-Italian	25.8% (207)	23.6% (2 563)
PREVIOUS PREGNANCIES		
None	65.7% (528)	56.9% (6 182)
One or more	34.3% (276)	43.1% (4 686)
PREVIOUS SPONTANEOUS ABORTIONS		
Yes	18.9 % (152)	18.1% (1 970)
No	81.1% (652)	81.9% (8,898)
PREVIOUS TERMINATIONS OF PREGNANCY		
Yes	5.8% (47)	9.9% (1 015)
No	94.4%(757)	90.1% (9 853)

SD*: Standard deviation; **Data from regional statistic service

DISCUSSION

The objective of this study was to analyse the reasons for seeking genetic counselling during pregnancy, excluding age related problems, and to consider the medical-technical and procedural consequences.

When anomalies in the foetus are detected during pregnancy (e.g. by ultrasound), multidisciplinary services have been implemented to manage the risk even if healthcare systems differ between countries and within the same country. Nevertheless, families or physicians may ask for a specialized genetic counselling after detection of abnormalities in the foetus to determine the risk of any intellectual disability or

TABLE 2

COUNSELLING ISSUES AND GESTATIONAL AGE (WEEKS) AT COUNSELLING FOR RISK FACTORS DETECTED DURING PREGNANCY (ITALIAN AND NON-ITALIAN)

		GESTATIONAL AGE AT COUNSELLING (WEEKS)				
NATIONALITY	COUNSELLING ISSUES	≤13	14-18	19-24	≥25	TOTAL
ITALIAN	Maternal exposure	119	9	4	2	134
	Chromosomal abnormalities in the foetus	23	26	37	2	88
	Congenital abnormalities (echographically detected)	11	4	17	7	39
TOTAL ITALIANS		153	39	58	11	261
NON-ITALIAN	Maternal exposure	26	9	3	0	38
	Chromosomal abnormalities in the foetus	3	5	8	1	17
	Congenital abnormalities (echographically detected)	1		5	3	9
TOTAL NON-ITALIANS		30	14	16	4	64
TOTAL		183	53	74	15	325

TABLE 3

COUNSELLING ISSUES AND GESTATIONAL AGE (WEEKS) AT COUNSELLING FOR PRE-EXISTING RISK FACTORS (ITALIAN AND NON-ITALIAN)

		GESTATIONAL AGE AT COUNSELLING (WEEKS)				
NATIONALITY	COUNSELLING ISSUES	≤13	14-18	19-24	≥25	TOTAL
ITALIAN	Consanguineity	6				6
	Chromosomal abnormalities	43	4	1		48
	Heritable conditions	223	44	11	7	285
	Multifactorial/heterogeneous conditions	77	11	3		91
TOTAL ITALIANS		349	59	15	7	430
NON-ITALIAN	Consanguineity	8	10	1	1	20
	Chromosomal abnormalities in relatives	6	3	1		10
	Heritable conditions	42	44	26	11	123
	Multifactorial/heterogeneous conditions	18	6			24
TOTAL NON-ITALIANS		74	63	28	12	177
TOTAL		423	122	43	19	607

TABLE 4

DIAGNOSTIC STATUS AT GENETIC COUNSELLING FOR RISK FACTORS DETECTED DURING PREGNANCY

NATIONALITY	ITALIAN				NON-ITALIAN				
DIAGNOSTIC STATUS	CLINICALLY DEFINED	GENETICALLY DEFINED	TO BE STUDIED	TOTAL	CLINICALLY DEFINED	GENETICALLY DEFINED	TO BE STUDIED	TOTAL	TOTAL
Counselling issues									
Maternal exposure	31		103	134	16		22	38	172
Chromosomal abnormalities in the foetus		74	14	88		11	6	17	105
Congenital abnormalities echographically detected	31	1	7	39	6		3	9	48
TOTAL	62	75	124	261	22	11	31	64	325

Clinically defined: a precise clinical diagnosis with no genetic mutation identified
Genetically defined: complete clinical and genetic diagnosis (mutation or chromosomal abnormality characterised)
To be studied: a precise clinical diagnosis was not defined

TABLE 5

DIAGNOSTIC STATUS AT GENETIC COUNSELLING FOR RISK PRE-EXISTING RISK FACTORS

NATIONALITY	ITALIAN				NON-ITALIAN				
DIAGNOSTIC STATUS	CLINICALLY DEFINED	GENETICALLY DEFINED	TO BE STUDIED	TOTAL	CLINICALLY DEFINED	GENETICALLY DEFINED	TO BE STUDIED	TOTAL	TOTAL
Counselling issues									
Consanguineity			6	6			20	20	26
Chromosomal abnormalities in relatives	5	35	8	48	2	5	3	10	58
Heritable conditions	108	86	91	285	49	19	55	123	408
Multifactorial/ heterogeneous conditions	45	2	44	91	12		12	23	115
TOTAL	158	123	149	430	63	24	90	176	607

Clinically defined: a precise clinical diagnosis with no genetic mutation identified
Genetically defined: complete clinical and genetic diagnosis (mutation or chromosomal abnormality characterised)
To be studied: a precise clinical diagnosis was not defined

morphological abnormalities and to discuss risks for future pregnancies. In our study, these issues are 34.9%, are heterogeneous and represent a significant commitment for genetic services.

Little has been established in the Emilia Romagna Region regarding the timing of counselling for hereditary conditions during pregnancy and the policy for primary health care [1-3, 9, 18]. In our dataset about 35% of the women were more than 14 weeks pregnant at the first consultation and among these 56.4% had a family history of genetic disease. Late referrals absorb considerable resources, provide less than optimum solutions for the couple and can pose significant ethical and organisational challenges involving checking medical records

TABLE 6

CATEGORIES OF RISK FOR THE FOETUS DETERMINED AFTER COUNSELLING FOR RISK FACTORS DETECTED DURING PREGNANCY OR EXISTING PRIOR TO PREGNANCY FOR ITALIANS AND NON-ITALIANS

DURING PREGNANCY	ND*	NS§	5-10%	>10%	TOTAL
NATIONALITY: ITALIAN					
Counselling issues					
Maternal exposure	9	117	7	1	134
Chromosomal abnormalities in the foetus	7	41		40	88
Congenital abnormalities echographically detected	21	14	1	3	39
TOTAL	**37**	**172**	**8**	**44**	261
NATIONALITY: NON-ITALIAN					
Counselling issues					
Maternal exposure	3	35			38
Chromosomal abnormalities in the foetus		7	1	9	17
Congenital abnormalities echographically detected	5	2		2	9
TOTAL	**8**	**44**	**1**	**11**	64
PRE-EXISTING	**ND***	**NS§**	**5-10%**	**>10%**	**TOTAL**
NATIONALITY: ITALIAN					
Counselling issues					
Consanguinity	1	4		1	6
Chromosomal abnormalities in relatives	3	36		9	48
Heritable conditions	27	163	1	94	285
Multifactorial/heterogeneous conditions	32	26	3	5	94
TOTAL	**63**	**229**	**4**	**109**	433
NATIONALITY: NON-ITALIAN					
Counselling issues					
Consanguinity	2	18			20
Chromosomal abnormalities in relatives		7	1	2	10
Heritable conditions	8	79		36	123
Multifactorial/heterogeneous conditions	8	15	1		24
TOTAL	**18**	**119**	**2**	**38**	177

ND*: reliable information not available; NS§: no genetic disorder or birth defects reported or no influence of the history on foetal risk

and, depending on the condition, examining family members and/ or requesting genetic tests.

The study also highlights a problem of equity in access to services. Deciphering information regarding family history from non-Italians is often complex for cultural and linguistic reasons [21]. Non-Italians tend to arrive at counselling late and with little information available thus requiring more work and technical resources to define the condition clinically and genetically.

An accurate genetic diagnosis is the essential step in quantifying reproductive and foetal risk and this occurred in 25% of cases [18, 19]. Patients and their families whose conditions are undiagnosed can feel isolated and studies [18] have described the importance of a diagnosis for patients, their families, clinicians and others involved in their care.

The high percentage of cases in the dataset (21.7%) with a *priori* risk of at least 10% for the unborn child highlight the need to promote preconception care pathways and programs for the referral of women with reproductive risks to a specialist genetic centre.

Comprehensive preconception care requires the assessment of a woman's personal health, health behaviours and past medical history as well as the couple's family medical history. The implementation of routine family

history collection in general practice to identify families at risk is needed along with the development of the role of the General Practitioner and other specialists in the timely and appropriate referral for genetic counselling. A multigenerational medical family history, recorded as a pedigree, is an effective tool [12] in preconception counselling to identify couples at risk. Interpretation of a pedigree can also identify other relatives who may benefit from genetic evaluation. Health pathways need to be established and greater awareness created in both health professionals and couples of reproductive age to enable timely referral to genetic counselling for those at potential risk.

CONCLUSIONS

Through analysis of the current situation and an appraisal of the organisational challenges for the development of timely clinical services we hope to aid the formulation of public health policy regarding access, equity and funding in the Emilia Romagna Region healthcare referral system.

Referral for genetic counselling during pregnancy can require considerable resources and pose significant ethical and organizational challenges. New models of providing pregnancy care in the community need to be developed.

General practitioners and gynaecologists have an important role in the referral and in the defence of equity of access and a more structured approach to the participation of medical geneticists in primary practice should be considered. Shared and established protocols along with health policies including prevention strategies are important to overcame many of these problems.

ACKNOWLEDGEMENTS: *the Authors are deeply indebted to Dr Amanda Neville for helpful comments and English revision of the paper.*

GRANTS: *Ricerca Finalizzata ex art. 12 e 12 bis del D.Lgs 502/92. Progetto N 3 "Sviluppo linee guida per offrire test genetici nelle gravidanze a rischio: implementazione di processi di valutazione dei test genetici esercizio 2007".*

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