Research

FOETAL CHROMOSOMAL MICROARRAY GENETIC SCREENING FOR MINOR ULTRASOUND ANOMALIES AFFECTS MATERNAL REPRESENTATIONS AND EMOTIONAL STATE: AN EXPLORATORY STUDY

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Foetal chromosomal microarray genetic screening for minor ultrasound anomalies affects maternal representations and emotional state: an exploratory study

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Introduction

Foetal ultrasound screening may detect a "soft marker", i.e. a feature that is not per se a birth defect, but whose presence increases the risk of a chromosomal anomaly. In such cases, amniocentesis for cytogenetic testing is currently offered to rule out a foetal chromosomal abnormality. In the majority of cases, the cytogenetic result and ultrasound follow-up are reassuring and the neonate is doing well. Such a falsely positive ultrasound screening may not be as benign as it seems. It may affect negatively the mother's representations of the infant and her emotional status, eventually impairing mother-infant interaction (1-7). Alteration of mother-child early interactions may impinge on short term (8-10) and arguably long term child development (11, 12).

Foetal chromosomal microarray analysis (CMA) tends to complement standard G-band karyotyping. It allows for the detection of small pathogenic chromosomal variants that are undetectable using standard cytogenetic analysis (13-15). One of the greatest challenges presented by CMA is detection of chromosomal Variants Of Unknown clinical Significance (VOUS) (16, 17) making genetic counselling particularly complex (18). When foetal soft markers are found, the psychological impact of offering CMA in addition to standard karyotyping is uncertain. It might reduce maternal anxiety by decreasing the perceived risk of missing a genetic anomaly. Alternatively, it might increase maternal anxiety due to the complexity of counselling on VOUS.

Our goal was to analyse maternal anxiety, depression and maternal representations of the infant in a short series of pregnancies with

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Conflict of Interest
None declared. All the authors declare that they have no conflict of interest.

Author Contributions
Conceived and designed the experiments: SV-S, MDo, MDe, IM. Performed the experiments: MDe SV-S MD. Analyzed the data: NB SV-S MDe MDo DC. Contributed reagents/materials/analysis tools: SV-S, NB, YV, IM. Wrote the paper: SV-S, MDo, NB, MDe, DC. Genetic expert: IM. Ultrasound experts: MD, YV.

All the authors reviewed and approved the final version of the manuscript

Ethical Approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local Ethical Committee (CPPIDF6) approved the study.

sonographic soft markers, in which foetal standard G-band karyotyping and chromosomal microarray analysis (CMA) were reassuring. We compared this CMA group to controls without any foetal abnormality, and to a previously published series of women with foetal sonographic soft markers who had foetal standard G-band karyotyping without CMA (1).

Patients and methods

The local institutional review board (*Comite de Protection des Personnes "Ile de France VI")* approved the study (n° 11.06.2014). Written informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

Participants

We recruited CMA soft marker pregnant women and normal controls in the Obstetric departments of Pitie-Salpetriere and Necker Hospitals, Paris, France from August 2014 to December 2014.

Mothers with foetal soft markers and CMA were selected by reviewing prenatal medical records. Inclusion criteria were: singleton pregnancy, normal neonatal outcome, no history of psychiatric disorder, no history of foetal or neonatal loss including termination of pregnancy for foetal anomalies, foetal karyotyping and CMA indicated for sonographic "soft markers" i.e. mild anomalies that would not indicate any specific perinatal management would foetal karyotyping and CMA is reassuring. Non-French speakers and women under 18 were excluded. After delivery, one of the authors (M De) contacted mothers in the postnatal maternity ward and asked them if they would like participate. After written consent, the interviews were conducted within two weeks after delivery.

Normal controls were selected post-partum, during their hospital stay, based on the following criteria: singleton pregnancy, no history of psychiatric disorder, no history of foetal or neonatal loss including termination of pregnancy for foetal anomalies, uneventful pregnancy. They were matched with CMA mothers for age and parity. Non-French speakers and women under 18 were excluded. After delivery, one of the authors (M De) contacted mothers in the postnatal maternity ward and asked them if they would like participate. After written consent, the interviews were conducted within two weeks after delivery.

Controls with foetal soft markers, standard G-band karyotyping but no CMA were part of a previously published study (1) in which maternal rep resentations were collected with the same methods in the early post-partum.

Methods

Maternal representations were assessed using a semi-structured interview adapted from the Interview of Maternal Representations during pregnancy (IRMAG) (19-21). The IRMAG explores changes that occur in the mental representations of the woman, regarding herself as a mother, or her future child, in relation to the following areas: daily events that primarily concern mother–child interaction during the first months of the infant's life; perceptions, emotions, parental fantasies about the child; and future expectations (19, 21). This semi-structured interview explores maternal representations in the perinatal period. The narrative pattern is analysed using a 5-point scale for each of seven dimensions: richness of perceptions, openness to change, affective involvement, coherence, differentiation, social referencing, and emergence of fantasies. These dimensions are content-free in the sense that they reflect formal features of the narratives Interviews were audio-recorded, lasted 60-90 minutes, and a written transcript was made. Scales of 1 (poor), 2 (limited), 3 (moderate), 4 (considerable), and 5 (very marked) were used to code each dimension.

Based on this first rating, we applied a second coding algorithm resulting in the mother's transcript being classified into one of the 3 categories: integrated/balanced, restricted/disengaged and non-integrated/ambivalent. This gross classification was the only data reported in the previously published series of mother with SM without CMA that focused on early infant-mother interaction (1). In the integrated/balanced category, women give a consistent picture of their experience in the context of their personal history; they show that they are open to changes and to doubts. Pregnancy represents a stage of their personal development and the fulfilment of their personal identity. In the restricted/disengaged category, interviews are characterized by high emotional control and inhibition on the part of the woman. Impersonality, poor fantasies, and abstractness prevail, as shown by the reported episodes that do not transmit the sense of a personal and affective experience. In the non-integrated/ambivalent category, interviews show a poorly coherent narration in which different tendencies toward motherhood and the child coexist, with excessive involvement and a struggle to impose distances.

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Information may be rich and also emotionally nuanced; nevertheless the description is not well-organized overall. (19) We could not blind the narrative analysis to whether or not women were exposed to prenatal testing since the history of the pregnancy was part of the narrative itself.

Anxiety was assessed using the Covi clinical scale (maximum score=12; threshold for disorder=6) (22, 23). Depression was assessed using the Raskin clinical scale (maximum score=12; threshold for disorder=6) (24). DSM-IV-TR symptoms for Major Depressive Episode were assessed when the Raskin score was above the clinical threshold.

We assessed the comparability of the groups based on demographic and obstetrical variables as well as life events during pregnancy. Life events were collected using the Sensations During Pregnancy and Life Event Questionnaire (25, 26) as well as general data (parity, socio-demographic status, and medical history).

Statistical Analysis

Data were analysed using the R software, version 2.10. To compare the three groups, we used the Fisher's Exact Test for qualitative variables and the Kruskal Wallis test for quantitative variables. To compare subgroups two by two, we used a post-hoc Nemenvi-Damico-Wolf-Dunn Test and Bonferroni adjustment. The significance level of the statistical tests was set < to 0.05.

Results

Out of 15 potentially eligible women to CMA group, 3 declined to participate, 1 was not included because her baby had severe growth retardation, and one delivered elsewhere. Eventually, 10 women were included in the CMA group. Out of 12 eligible control women, 1 declined to participate, 1 was excluded because of a history of psychiatric disorder, and 10 were included.

The Soft Marker with CMA group did not differ significantly from the normal control group and from the previously published soft markers (SM) group without CMA (Table 1) for maternal age, parity, birth weight, marital status, education level, obstetrical history and delivery mode. Gestational age at prenatal diagnosis was similar in the CMA group and in the previously published SM group without CMA. Babies' gender ratio was similar in the three groups.

Table 1. Sociodemographic data

We found no significant difference between the three groups: women with soft markers having chromosomal microarray analysis (SM with CMA), women with soft markers having no chromosomal microarray analysis (SM without CMA), and women without any sonographic anomaly (controls).

	SM with CMAn=10		SM without CMA n=18		Control n=10		
	mean	**sd**	**mean**	**sd**	**mean**	**sd**	p
Maternal age (y)	33.4	5.7	32.2	3.9	31.1	3.6	0.459
Gestational Age at Birth (w)	39.4	1.8	39.1	2.2	39.7	0.8	0.988
Gestational age at prenatal diagnosis (w)	17.1	6.6	21.3	5.5	NA	NA	0.109
Birthweight (g)	3342	568	3348	551	3373	349	0.986
Marital Status							0.543
Single (n, %)	1 (10)		1 (6)		0 (0)		
In couple (n, %)	4 (40)		11 (61)		4 (40)		
Maried (n, %)	5 (50)		6 (33)		6 (60)		
Academic level							0.955
Undergraduate (n, %)	1 (10)		1 (6)		1 (10)		
Bachelor (n, %)	1 (10)		2 (11)		0 (0)		
University degree (n, %)	8 (80)		15 (83)		9 (90)		
Pare during pregnancy							0.923
Nullipara (n, %)	3 (30)		8 (44)		5 (50)		
Primipara (n, %)	5 (50)		7 (39)		3 (30)		
Multipara (n, %)	2 (20)		3 (17)		2 (20)		
Obstetrical History							0.917
None (n, %)	5 (50)		9 (50)		6 (60)		
At least one major event (n, %)	5 (50)		9 (50)		4 (40)		
Delivery							0.493
Vaginal (n, %)	8 (80)		12 (67)		9 (90)		
Caesarean (n, %)	2 (20)		6 (33)		1 (10)		

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Ultrasound features leading to prenatal diagnosis are displayed in table 2. In all cases with SM, the prenatal diagnosis work up was considered reassuring. All foetal karyotypes and CMA were normal. All perinatal outcomes were favourable as defined by a live born free from any detectable birth defect.

Table 2. Prenatal Ultrasound findings

In all cases, the foetus was eventually considered as unaffected by a severe disorder, based on prenatal diagnostic workup and sonographic follow up.

	SM with CMA (N=10)	SM without CMA (N=18)
Enlarged 1st trimester nuchal translucency	5	3
Femur lenght <5th centile	2	0
Hyperechogenic bowel	1	6
1rst trimester Umbilical hernia	1	0
Suspected fetal heart defect	1	0
Mild ventriculomegaly	0	3
Short nasal bones	0	1
Pyelectasis	0	5

The number of life and stress events scored by the stress events questionnaire was significantly greater in the SM with CMA group (mean=11.3, SD=3.2) than in controls (mean=6, SD=2.9, $p<0.02$). It was similar in the SM with CMA group and the SM without CMA group (mean=8, SD=4.8, p=0,31).

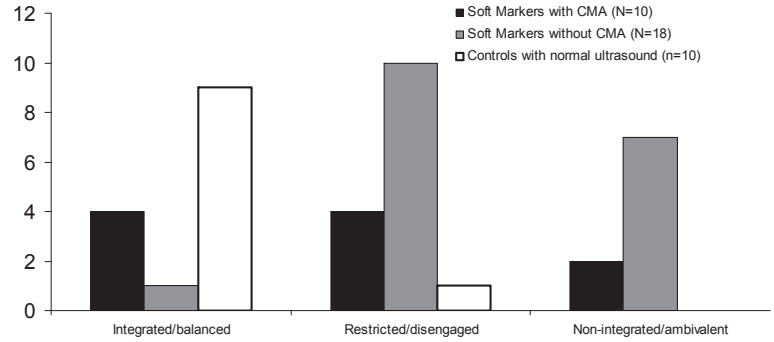
The Raskin depression score was significantly greater in the SM with CMA group (mean: 3.8; SD: 1.8) than in controls (mean: 2; SD: 1.2; $p<0.05$). The Raskin depression score was similar in the SM with CMA group and in the historical series of SM without CMA (mean: 3.6; DS: 1.7).

Regarding anxiety, the STAI was slightly but not significantly greater in the SM with CMA group (mean: 41.3; SD: 10.8) than in controls (mean: 37.8; SD: 11). Similarly, the COVI anxiety score was slightly but not significantly greater in the SM with CMA group (mean: 5.5; SD: 1.3) than in controls (mean 4.3; SD: 1.3). In the historical series of SM without CMA, the mean COVI score was 4.7 (SD: 1.7)

Maternal representations in the SM with CMA group and in the SM without CMA group were more frequently altered than in controls, with more "Restricted/disengaged" and "non-integrated/ambivalent" representation patterns. The rate of Integrated/balanced representations was 4/10 in women undergoing CMA vs. 9/10 in controls and 1/18 in women with SM but without CMA ($p<0.05$). (Figure 1)

Figure 1. Categories of aternal representations

Figure shows raw numbers of patient per category, split by group (SM with CMA, SM without CMA, controls without SM). The distribution of categories between the 3 groups was significantly different ($p<0.05$, Fisher's Exact Test): women with soft markers having chromosomal microarray analysis (SM with CMA), women with soft markers having no chromosomal microarray analysis (SM without CMA), and women without any sonographic anomaly (controls).



The detailed dimensions of maternal representations are displayed in on table 3 and figure 2. In the SM with CMA group, four dimensions (Richness of perceptions, Coherence, Social referencing, and Emergence of fantasies) where significantly altered in comparison with controls. Affective engagement and Differentiation were not significantly altered. In the SM without CMA group, all dimensions where significantly altered in comparison with controls.

Figure 2. Maternal representations: dimension analysis

Figure shows mean score and standard deviation for each dimension of maternal representation, split by group (SM with CMA, SM without CMA, controls without SM)

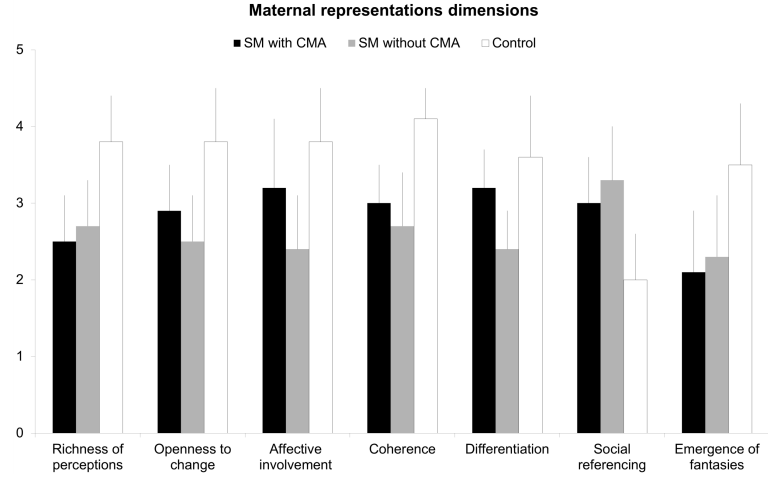


Table 3. Dimensions of Maternal representations

Overall, the mean scores for each dimension were significantly different between the three groups (p<0.05, Kruskal Wallis test): women with soft markers having chromosomal microarray analysis (SM with CMA), women with soft markers having no chromosomal microarray analysis (SM without CMA), and women without any sonographic anomaly (controls). When comparing the mean score for each dimension between soft marker patients without CMA and controls, we found a significant alteration for all dimensions (p<0.05 post-hoc Nemenyi-Damico-Wolfe-Dunn Test). When comparing the mean score for each dimension between soft marker patients with CMA and controls, we found a significant alteration for "Richness of perceptions", "Coherence", "Social referencing", and "Emergence of fantasies" (p<0.05 post-hoc Nemenyi-Damico-Wolfe-Dunn Test).

	Soft Markers with CMA (N=10)		Soft Markers without CMA (N=18)		Controls (n=10)		p	Adjusted p (Bonferroni)
	mean	sd	mean	sd	mean	sd		
Richness of perceptions	2.5	0.6	2.7	0.6	3.8	0.6	<0.001 (a,c)	<0.01 (a,c)
Openness to change	2.9	0.6	2.5	0.6	3.8	0.7	<0.001(c)	<0.01(c)
Affective involvement	3.2	0.9	2.4	0.7	3.8	0.7	<0.001(b,c)	<0.01(b,c)
Coherence	3	0.5	2.7	0.7	4.1	0.4	<0.001(a,c)	<0.01(a,c)
Differentiation	3.2	0.5	2.4	0.5	3.6	0.8	<0.001(b,c)	<0.01(b,c)
Social referencing	3	0.6	3.3	0.7	2	0.6	<0.001(a,c)	<0.01(a,c)
Emergence of fantasies	2.1	0.8	2.3	0.8	3.5	0.8	<0.005(a,c)	0.018 (a,c)

a: soft markers with CMA vs. controls
b: soft markers with CMA vs. soft markers without CMA
c: soft markers without CMA vs. controls

Discussion

Our results suggest that minor sonographic anomalies referred to as soft markers (SM) alter maternal representations and emotional status, regardless of whether or not the prenatal diagnostic work up includes CMA.

Clinical depression scores were significantly greater in women with SM than in controls. In previous studies (1, 3, 7, 27, 28) anxiety levels were greater in women with foetal sonographic anomalies than in controls. Surprisingly in this study, we found no significant difference in anxiety scores between women with SM and controls. This might be explained by the fact that the mean anxiety score in the control group of the present study was relatively high, greater (mean=4.3) than in the control group in a previous paper (mean=2.1), underscoring the limitation of historical comparison (1). It could also be that anxiety decreased following the birth of a healthy child, whereas depression persisted because of prenatal disruption of maternal representations by the announcement of SMs (1, 29).

The strength of our study is that it shows for the first time the impact of the foetal chromosomal microarray analysis screening on maternal emotional state and representation. Its main weakness is its small size, partly explained by the comprehensive format of our protocol. Besides, we did not evaluate mother-infant interaction. However, maternal representation assessment is a clinically meaningful outcome, since perinatal maternal representations are related to post-natal mother-infant interaction. Altered perinatal maternal representations are associated with a wide spectrum of anomalies in child development (8, 9, 11, 30). Altered maternal representations are also associated with maternal depression, anxiety, and generally speaking with increased psychosocial risks (21).

From a psychodynamic point of view, our results support the widely accepted concept that prenatal events may alter maternal representations, and hold maternal involvement during fetal investigations. These phenomena are considered as causing substantial alterations in postnatal maternal involvement and early mother infant interactions (8, 29). The absence of psychological effect of the type of genetic test might be explained by the pre-eminence of ultrasound announcement in generating psychological distress, either because ultrasound refers to visible anomalies, or because it is the first traumatic event occurring during the screening process (1).

Abstract

Background: When ultrasound screening reveals a minor fetal abnormality or "soft marker"(SM), prenatal suspicion impairs maternal representations and emotional status, even after the birth of a normal child. Recently, chromosomal microarray analysis (CMA) was added to standard karyotyping as part of the diagnostic work up for SM, which may have made counseling more complex, thus increasing parental anxiety.

Objective: To assess if CMA would affect maternal emotions and representations differently than karyotyping alone.

Methods: We compared pregnant women with SM undergoing fetal karyotype plus CMA (n=10) to controls without any sonographic abnormality (n=10) and to pregnant women with SM who underwent conventional karyotyping only (n=18). Within one-week postpartum, we assessed: Covi anxiety scale, State Trait Anxiety Inventory (STAI), the Raskin depression scale, and the Interview of Maternal Representations during pregnancy (IRMAG), classifying representations

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as: Integrated/balanced, restricted/disengaged, or non-integrated/ambivalent. Results. All newborns were free from birth defects. In the CMA group, the mean depression score (3.8) was greater than in controls (2) ($p<0.05$). The rate of Integrated/balanced representations was 4/10 in women undergoing CMA vs. 9/10 in controls and 1/18 in women with SM but without CMA ($p<0.05$). Maternal representations lacked richness, coherence, social referencing and fantasies in SM cases compared with controls ($p<0.05$). In the CMA group, maternal representations however, were less altered than in SM cases with without CMA. Conclusion: Adding CMA to conventional karyotyping affected maternal emotions and representations in a similar way as conventional karyotype alone. Guidelines for the geneticist and the sonographer could to be developed to decrease the negative psychological impact of SM.

Keywords
Chromosomal microarray analysis.
Fetal soft marker.
Maternal representations.
Anxiety.
Depression.
Prenatal diagnosis.
Ultrasound screening.

From a genetic point view, our results are reassuring. When CMA became part of routine prenatal diagnostic workup for soft markers, geneticists were concerned with the potential psychological impact of this technique (16, 17). They feared that announcing the risk of either a variant of unknown significance VOUS or a cryptic chromosomal abnormality with poorly known clinical consequences might be devastating for future parents. Another concern was that the complexity of prenatal counselling on CMA would increase parental anxiety more than prenatal counselling on standard karyotype. The interpretation of our results however, is limited by the fact we found no prenatal VOUS. The absence of increased psychological impact of foetal CMA may also be due to the fact that pregnant women remained unaware of the difference between the potential drawbacks of foetal CMA and those of a conventional foetal karyotype, as some of them declared (data not shown).

Conclusion

For all its limitations, our study suggests that finding a sonographic soft marker interferes negatively with maternal representations and emotions, but that the type of genetic workup, CMA or conventional karyotyping, has no major psychological impact. Guidelines for the geneticist and the sonographer could be developed to decrease the negative psychological impact of the prenatal finding of sonographic soft markers.

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Conflict of Interest

All the authors declare no conflict of interest concerning this study.

Take home message: The finding of a fetal sonographic soft marker alters maternal emotions and representations of the child despite reassuring genetic results and a normal neonatal outcome, regardless of the genetic analysis technique.

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