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GENETICS

Impact of maternally derived meiotic aneuploidies on early embryonic development in vitro

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Abstract

Purpose To assess early embryonic developmental potential of embryos affected by maternally inherited meiotic aneuploidies.
Methods This observational, descriptive study includes 930 oocytes from 151 patients which were retrospectively analyzed by combining the morphological assessment with the genetic results from polar body diagnosis.
Results Of 930 oocytes examined, 566 (60.9%) were tested aneuploid. Developmental potential until cleavage stage was not affected by trisomies or monosomies (69.6% vs. 77.1%, $p=0.75$). However, trisomies significantly more often resulted in top quality cleavage stage embryos compared to monosomies (20% vs. 17.6%, $p=<0.01$). Top quality blastocysts were more likely to be euploid than aneuploid (52.4% vs. 47.6%, $p=0.032$). Additionally, significantly more aneuploid embryos resulted in developmental arrest compared to euploid embryos (15.3% vs. 6.7%, $p=0.003$). Overall, there was no significant difference in the frequency of trisomies and monosomies in blastocyst stage embryos. (28.3% vs. 28.2%; $p=0.81$). In contrast to earlier developmental stages, distribution of trisomies and monosomies did not differ in top quality blastocysts (8.3% vs. 5.3%, $p=0.32$). However, certain chromosomal abnormalities showed a higher potential to develop into a top-rated blastocyst. These included monosomies 2, 5, 8, 10, 16, 17, 20, 21, and 22 and trisomies 2, 4, 5, 8, 9, 10, 11, 12, 13, 16, 17, 18 and 20.
Conclusion Meiotically induced maternal aneuploidies have different effects on early embryonic development. While no difference in developmental potential between monosomies and trisomies could be observed in blastocysts, cleavage stage quality was significantly affected by chromosomal aneuploidies.

Keywords PGT-A · Polar bodies · Aneuploidies · IVF · Embryo quality

Background

For various organic, pathophysiological, and psychological reasons, natural conception may be challenging. Since social framework conditions have changed in a way, that family planning tends to be pushed to a more advanced age, fertility rates decline and an increasing number of patients depend on assisted reproduction [1]. One major factor of age related fertility decline is that oocytes from women of advanced age are more likely to be affected by chromosomal maldistributions, resulting in a higher rate of early miscarriage or Infertility [2].

About 10–30% of all fertilized oocytes are aneuploid, making it the leading known cause of miscarriage. Aneuploidy results predominantly due to failures in chromosome segregation in female meiosis and the frequency of these errors increases dramatically as women age. It is estimated that only a small percentage of < 1% meiotic errors are of paternal origin. Analyzing the polar bodies allows to receive information on meiotically derived aneuploidies of the oocyte, therefore only maternally inherited aneuploidies can be detected [3, 4].

Polar body biopsy (PBB) is understood to be a safe method of preimplantation genetic testing (PGT) without impacting morphokinetic parameters of early embryonic development. It is less invasive than trophectoderm biopsy or blastomere biopsy and does not impair the embryos developmental potential, as polar bodies are a byproduct of oocyte formation and are not required for further embryo development [5].

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Although the live birth rate is not significantly higher applying PBB to invitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment, two studies [6, 7] independently found that the miscarriage rate was lower implementing PBB.

In conventional IVF/ICSI cycles, embryos for transfer in utero are selected according to morphological parameters such as blastocyst expansion, cell number and fragmentation rate. Embryos that show optimal development in all morphological parameters at the blastocyst stage are classified as top embryos which are considered suitable for transfer in utero.

To date, no study investigated the impact of maternally derived meiotic aneuploidies on early embryonic development. The aim of this study was to compare the morphological developmental status of meiotically aneuploid embryos at day three and day five post-fertilization.

Methods

Study design and settings

This study was conducted as a single-center retrospective, observational, descriptive study.

930 oocytes from 151 patients undergoing IVF/ICSI treatment and polar body diagnosis between 2016—2020 were retrospectively analyzed by combining the genetic results from polar body diagnosis and the morphological assessment that has been documented by embryologists.

As this study was conducted in Austria, PGT is tightly controlled and only permitted to diagnose inheritable diseases. Consequently, polar body biopsy is the technology most frequently performed.

Inclusion / exclusion criteria

Inclusion criteria comprised female patients younger than 42 years who had polar body based preimplantation genetic testing for aneuploidies (PGT-A) performed between 2016–2020.

Exclusion criteria included patients requiring preimplantation genetic testing for monogenetic disorders (PGT-M), patients with balanced genetic translocations and male partners requiring testicular sperm extraction (TESE), respectively with a total sperm count < 2.000.000/ml.

Polar body biopsy

Depending on individual parameters like age, body mass index (BMI) and basal follicle-stimulating hormone (FSH), patients underwent ovarian hyperstimulation in the gonadotropin-releasing hormone (GnRH) agonist or GnRH antagonist protocol as described previously [8]. In short, determined by responder type (low responder, normal responder, and high responder), 100–300 IU gonadotropins were administered. In the following monitoring, follicle size and number were determined by ultrasound, as well as endometrial thickness and oestradiol levels. If mature follicles ≥ 18 mm could be identified, final oocyte maturation was induced with 5.000- 10.000 IU human chorionic hormone (hCG). Follicle pickup was performed in an ultrasound guided, transvaginal manner under short-acting anaesthesia. After oocyte pickup, ICSI was performed. 16–18 h after ICSI, first and second polar bodies were biopsied according to the European Society of Human Reproduction and Embryology (ESHRE) recommendations [9] and transferred together in a 0,2 ml microtube containing 2,5 µl phosphate-buffered saline as a medium. Within this, the pooled polar bodies were sent to laboratory for genetic testing using array-based comparative genomic hybridization (array-CGH analysis) as described previously [7].

Polar body diagnosis and subsequent statistic evaluation of the data is based on pooled polar body diagnosis of polar body one and two [7].

Embryo morphology assessment

Additionally to polar body diagnosis, all embryos were morphologically assessed on day three after fertilization (D3) and on day five after fertilization (D5) by an embryologist to choose the most suitable embryo for transfer and implantation.

After polar body biopsy, the embryos were stored in the New Brunswick™ Galaxy® 48R incubator (temperature: 37° Celsius, CO_2: 6%, oxygen: atmospheric) from 2016–2019. Due to lab-renewals, the G210 InviCell incubator (K Systems™) was used from 2020 on (temperature: 37° Celsius, CO_2: 6%, oxygen: 5%).

The blastocysts were closely monitored by embryologists for morphological criteria such as blastomere rate, blastocyst expansion, inner cell mass and grade of fragmentation. On day one, oocytes were checked for fertilization. Embryo scoring was performed on day two if embryo transfer was planned on day two. If embryo transfer was planned on day three or day five, embryo scoring was performed on day three. Cryopreservation was performed on day five or day six.

The embryo morphology assessment was followed by the *Istanbul consensus workshop on embryo assessment* by Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology [10].

In the event of euploidy and optimal development, the embryos were transferred in utero or cryopreserved.

Since many embryos with chromosomal abnormalities arrested or degenerated at earlier stages of embryonic development, there is not a morphological assessment of every

embryo by an embryologist at day three and day five after fertilization.

Statistical analyses and variables

Parameters used in the statistical evaluation included chromosomal integrity (euploidy, aneuploidy) and the affected chromosome in case of chromosomal aberration. The blastomere rate was assessed following a quality-rating from 1 (high quality) to 3 (low quality). Blastocyst expansion was rated from cleavage stage (not further developed), grade 1 (low quality) to 4 (high quality). Inner cell mass (ICM) was rated from 1 (high quality) to 4 (low quality).

The grade of fragmentation was assessed by using percentages from A: < 10% (good quality), B: 25% (medium quality) and C: > 50% (low quality).

The morphological development of each embryo in its first days was described by the following parameters: Blastomere rate, blastocyst expansion, inner cell mass and grade of fragmentation. This information was then linked to the individual data of genetic analysis gained from polar body biopsy, such as euploidy/ aneuploidy and the type of chromosomal aberration.

The collected data was descriptively analyzed by using Windows Excel and SPSS. The chi-square test was used to compare nominal data (e.g., euploid/aneuploid, monosomy/ trisomy) between the different groups and whether a pattern in the development and morphology of the embryo is recognizable in different aneuploidies by means of the parameters listed above.

Statistical significance has been proofed by applying the t-test (e.g., Aneuploidy distribution by patient age).

The null hypothesis was defined as a lack of aneuploid impact on early embryonic development, independent on the affected chromosome.

Primary and secondary study question

The primary study question was, which chromosomal constellations (euploid / aneuploid) result in a morphological top blastocyst at day five.

Secondary study question was, which chromosomal constellations (euploid / aneuploid) result in a morphological top embryo at day three.

Embryos that showed optimal development in the morphological assessment were classified as *top embryos*.

The evaluation by embryologists was strictly based on the *Istanbul consensus workshop on embryo assessment* by Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology[10], which uses morphological criteria such as blastomere rate, blastocyst expansion, inner cell mass and grade of fragmentation for grading.

Cleavage-stage embryos are considered as top-quality embryos by a number of four—eight cells, a mild degree of fragmentation (< 10%), the absence of multinucleation and a stage-specific cell size.

Top-quality blastocysts are defined by a hatched/hatching stage of development, a compacted and tightly adhered inner cell mass and a trophectoderm consisting of multiple cells forming a cohesive epithelium.

Results

In total, 930 oocytes from patients fulfilling the inclusion criteria were analyzed. 566 of those (60.9%) were aneuploid, 364 (39.1%) were euploid. With increasing age, an increase in aneuploid polar bodies could be observed (Fig. 1).

On average, euploid oocytes originated from younger women than aneuploid oocytes. (37.98 years vs. 39.23 years; $p = < 0.001$).

When analyzing the median oocyte age of the four most common aneuploidies 15, 16, 21 and 22, only minor differences in embryos with an aneuploidy of chromosome 21 (39.89 years), chromosome 16 (39.71 years), chromosome 22 (39.58 years) and chromosome 15 (39.54 years) could be observed.

Aneuploidy analyzation

In total, 566 aneuploid oocytes were analyzed within this study. These included 188 (33.2%) embryos with isolated monosomies, 145 (25.6%) embryos with isolated trisomies, five (0.9%) isolated sex chromosome aberrations and 228 (40.3%) oocytes with multiple chromosomes maldistributed (Fig. 2).

The four most common chromosomal abnormalities involved chromosomes 15, 16, 21 and 22.

Monosomies

Within all monosomies, the most represented were monosomy 16 (14.4%), monosomy 22 (13%), monosomy 21 (10.9%) and monosomy 15 (8.1%) (Fig. 3).

No monosomies occurred in oocytes from under 29-year-olds.

A total of 284 monosomies were identified within the assessed oocytes by polar body analysis. The number of embryos with isolated one or two monosomies was 188/284 (66.2%). Embryos with a combined aneuploidy e.g., monosomy + trisomy were not counted.

On day three after fertilization, 145/188 (77.1%) embryos with monosomies could be assessed by an embryologist. Of these, 33/188 (17.6%) top embryos were detected.

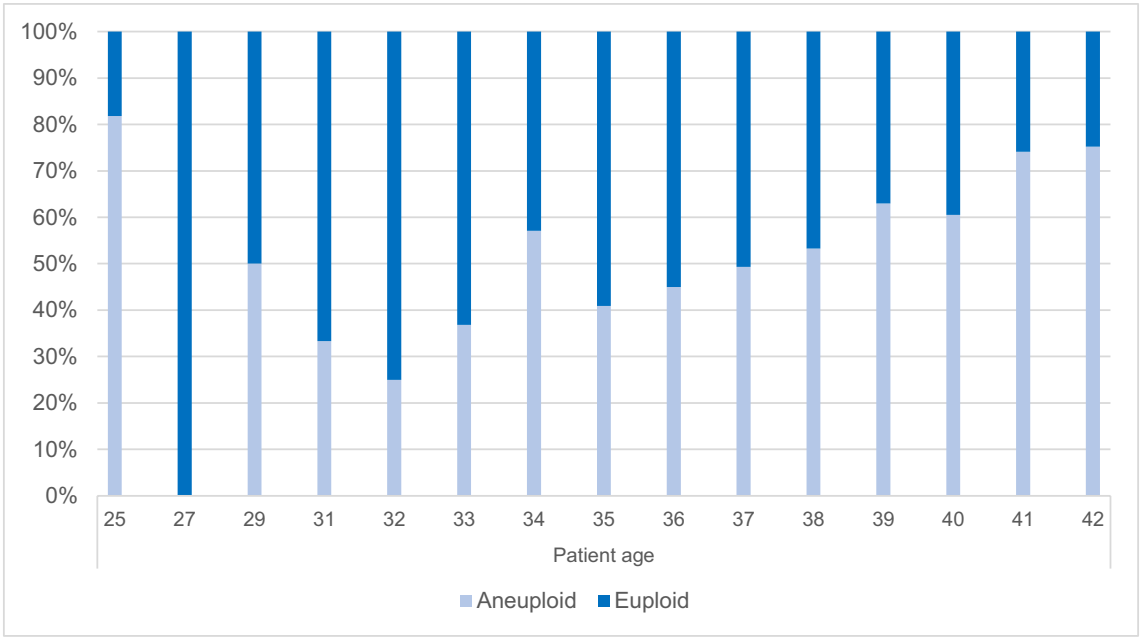

Fig. 1 Aneuploidy distribution curve in relation to patient age

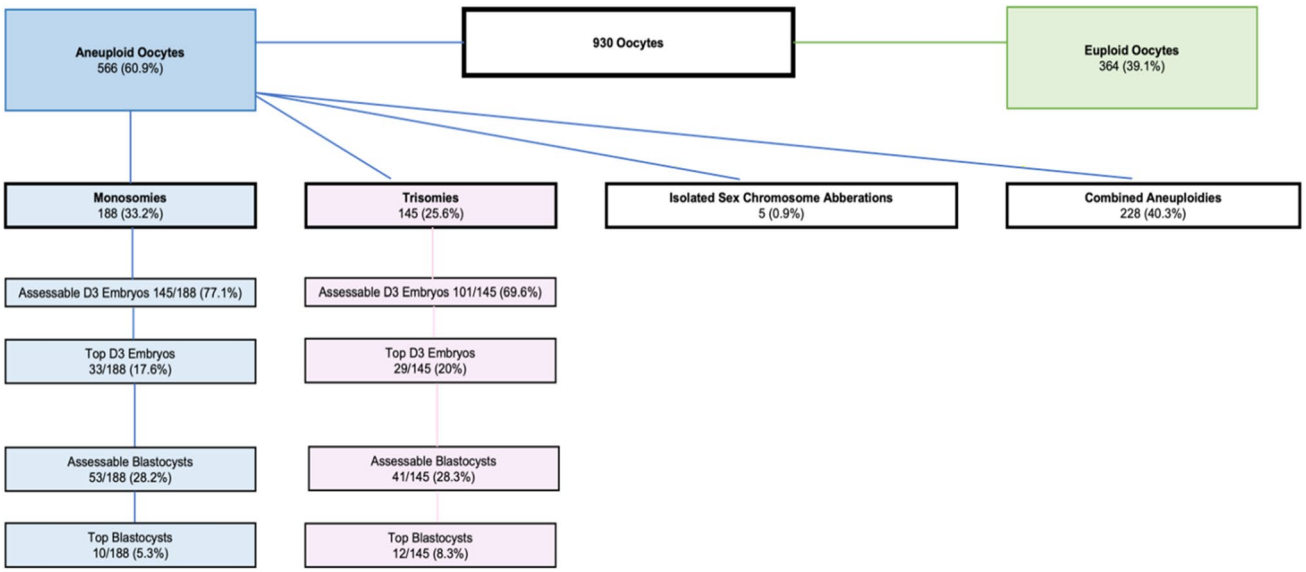

Fig. 2 Flowchart of aneuploidy analyzation

In the blastocyst stage, 53/188 (28.2%) embryos with monosomies could be assessed by an embryologist. 10/188 (5.3%) top quality blastocysts had single chromosomal reductions within monosomies 2, 5, 8, 10, 16, 17, 20, 21 and 22 (Supplementary table 1).

No top-quality blastocysts could be observed in monosomies 1, 3, 4, 7,9, 11, 12, 13, 14, 15, 18 and 19. All monosomy 4 and monosomy 1 embryos observed arrested in the cleavage stage (Supplementary table 1) (Table 1).

Trisomies

Within all trisomies, the most represented were trisomy 16 (13.1%), trisomy 22 (12.2%), trisomy 15 (11.4%) and trisomy 21 (10.5%) (Fig. 4).

As within monosomies, trisomy prevalence was increasing with female age.

A total of 237 trisomies were identified within the assessed oocytes by polar body analysis. The number of

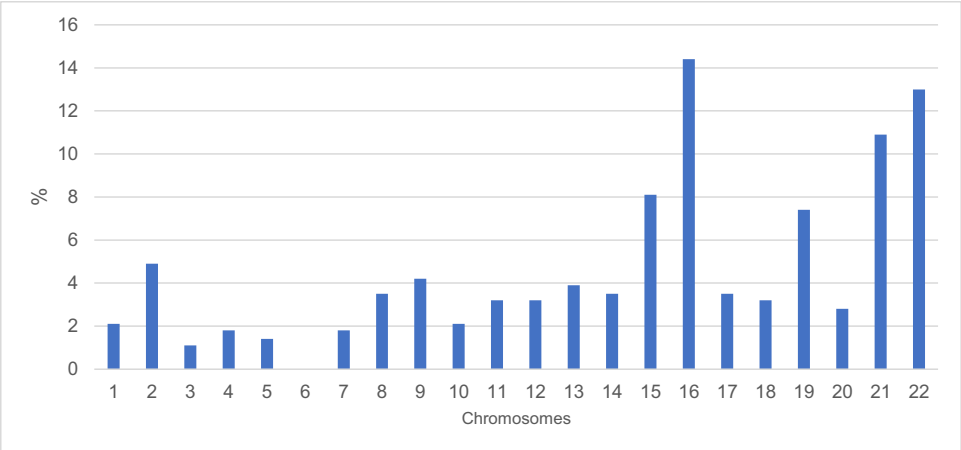

Fig. 3 Frequency of the individual chromosomal monosomies

Table 1 Comparison of monosomic and trisomic embryos in different developmental stages on day five

	deg	BI1	BI2	BI3	BI4	Kp	Cls	arr	Total
Trisomic Embryos	2	16	12	1	12	16	24	15	98
Monosomic Embrayos	3	32	11	0	10	16	39	11	122
Total	5	48	23	1	22	32	63	26	220

BI1: low quality blastocyst, **BI2:** intermediate quality blastocyst, **BI3:** good quality blastocyst, **BI4:** top quality blastocyst, **deg:** degenerated, **Cp:** compacted, **Cls:** cleavage stage, **arr:** arrested

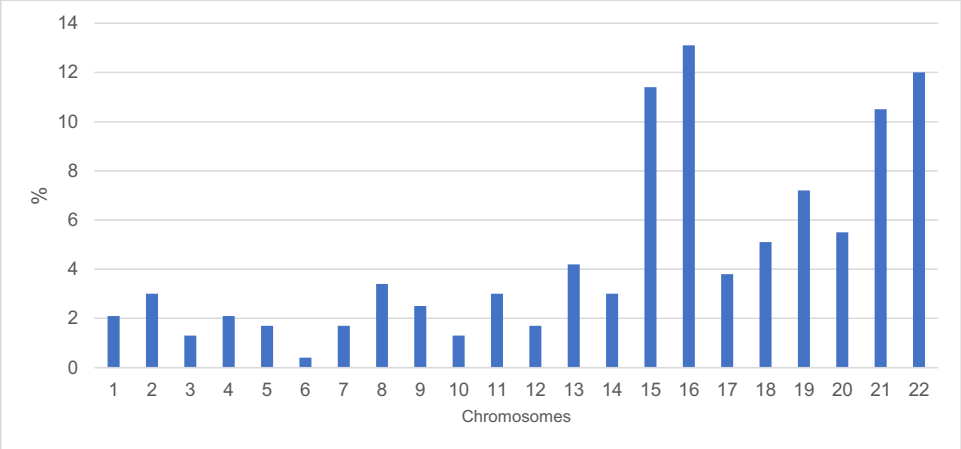

Fig. 4 Frequency of the individual chromosomal trisomies

embryos with isolated one or two trisomies was 145/237 (61.2%). Embryos with a combined aneuploidy e.g., monosomy + trisomy were not counted.

On day three after fertilization, 101/145 (69.6%) embryos with trisomies could be assessed by an embryologist. Of these, 29/145 (20%) top embryos were detected.

In the blastocyst stage, 41/145 (28.3%) embryos with trisomies could be assessed by an embryologist. 12/145 (8.3%) embryos were found in morphologically classified top embryos, including blastocysts with trisomies within chromosomes 2, 4, 5, 8, 9, 10, 11, 12, 13, 16, 17, 18, and 20.

No top-quality blastocysts could be observed in trisomy 1, 6, 7, 14, 15, 19 and 21 (Supplementary table 2).

Combined aneuploidies

Combined aneuploidy is defined as two different aneuploidies within one oocyte. This can consist of monosomies and trisomies. (Example: monosomy 15 + trisomy 21 OR monosomy 16 + monosomy 15 OR trisomy 19 + trisomy 16).

A total of 126 oocytes with combined aneuploidies were found.

As in single aneuploidies, chromosomes 15, 16, 20, and 21 were most frequently affected (Fig. 5).

The most common finding was a combination of monosomy and trisomy in 54/126 oocytes (42.9%) followed by double monosomy (monosomy + monosomy) in 41/126 oocytes (32.5%) and double trisomy (trisomy + trisomy) in 29/126 oocytes (23.0%).

Combined aneuploidies with a sex chromosomal aberration were found in only two oocytes (1.6%), both a monosomy 22, X0.

Maldistributed sex chromosome aneuploidies

Of 566 analyzed aneuploid oocytes, only seven (1.2%) were found with a maldistribution of sex chromosomes. Three (0.53%) of them a monosomy X (Turner-Syndrome), two (0.35%) of them a trisomy X (Triple-X-Syndrome) and two cases (0.35%) of a combined aneuploidy, monosomy 22, X0.

Multiple chromosomes maldistributed

Whenever more than two chromosomes of an oocyte were maldistributed, the genetic finding was titled "multiple chromosomes maldistributed". In this case, the individual chromosomal aberrations were not further described.

In general, an increasing number of oocytes with multiple chromosomes maldistributed could be observed with an increase in female age. (Fig. 6).

Blastocyst analyzation

Top quality blastocysts were more likely to be euploid than aneuploid (52.4% vs. 47.6%, $p = 0.032$) (Table 2).

Additionally, aneuploid embryos arrested in their development before blastocyst stage more often than euploid embryos (15.3% vs. 6.7%, $p = 0.003$) however,

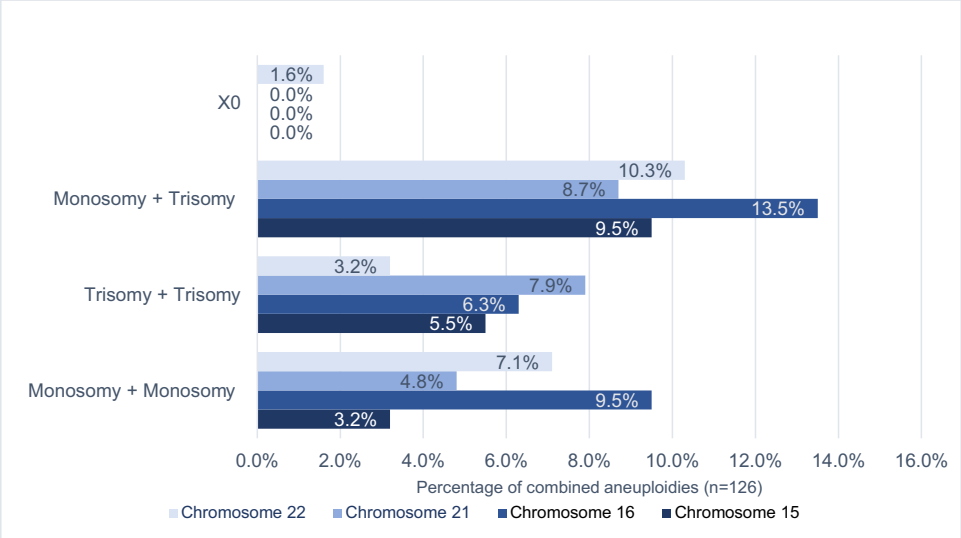

Fig. 5 Frequency distribution of combined aneuploidies

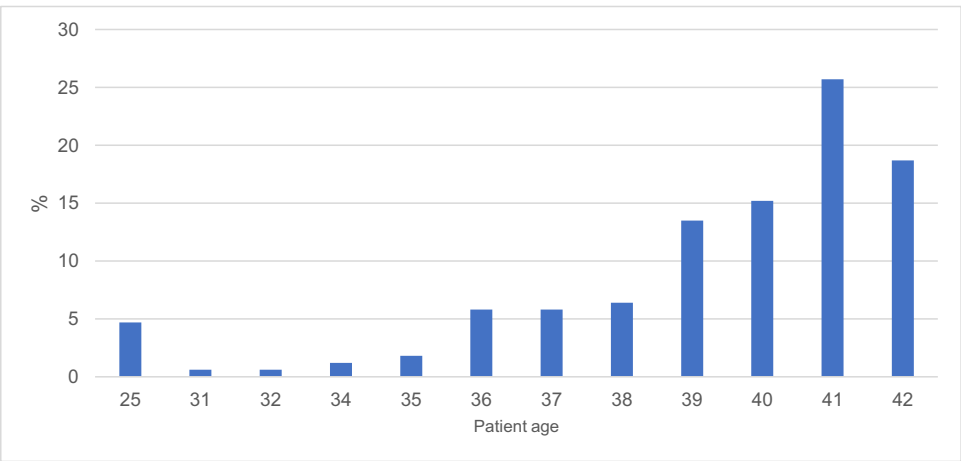

Fig. 6 Embryos with of multiple chromosomal maldistributions in relation to patient age

Table 2 Comparing aneuploid to euploid embryos at the blastocyst stage

		Aneuploid	Euploid	Total	*p*-Values
Degenerated	% of deg	61.9%	38.1%	100.0%	$p=0.032$
Bl1	% of Bl1	59.7%	40.3%	100.0%	$p=0.769$
Bl2	% of Bl2	50.0%	50.0%	100.0%	$p=0.075$
Bl3	% of Bl3	28.6%	71.4%	100.0%	$p=0.079$
Bl4	% of Bl4	47.6%	52.4%	100.0%	$p=0.032$
Compacted	% of Cp	58.1%	41.9%	100.0%	$p=0.588$
Total		60.1% ($n=360$)	39,9% ($n=239$)	100% ($n=599$)	

Bl1: low quality blastocyst, **Bl2:** intermediate quality blastocyst, **Bl3:** good quality blastocyst, **Bl4:** top quality blastocyst, **deg:** degenerated, **Cp:** compacted

comparing aneuploid and euploid embryos remaining in cleavage stage showed no statistical significance (28.6% vs. 24.7%, $p=0.436$).

Comparison of monosomies and trisomies regarding early embryo development potential

While no difference could be observed between isolated monosomies and trisomies in their developmental potential on day three (77.1% vs. 69.6% embryos with monosomies or trisomies reaching cleavage stage, respectively $p=0.75$) and blastocyst stage embryos (28.2% vs. 28.3%, embryos with monosomies or trisomies reaching blastocyst stage respectively, $p=0.81$), when comparing top quality day three embryos, significantly more embryos with trisomies developed to top-quality day three embryos than embryos with monosomies (17.6% vs. 20% embryos with monosomies or trisomies reaching top quality cleavage stage, respectively, $p=<0.01$) (Table 3). This effect could not be observed in top quality blastocysts (5.3% vs. 8.3%, embryos with monosomies or trisomies reaching top quality blastocyst stage, respectively, $p=0.32$).

Discussion

The present study, for the first time, investigated the effect of different chromosomal maternally inherited meiotic abnormalities on early embryonic development by comparing the genetic constellation with the morphological evaluation of the embryo. Morphological assessment was performed on day three and on day five after fertilization.

Within all assessable embryos on day three, no statistically significant difference in the frequency of trisomies and monosomies could be found.

However, day three embryos affected with trisomies compared to embryos with monosomies, significantly more often developed into top quality embryos.

Interestingly, top quality blastocysts showed a distinct distribution of chromosomes affected if trisomic or monosomic.

The assumption, that embryos with trisomies have more potential to develop into a morphologically top blastocyst than embryos with monosomies could not be proven statistically (8.3% vs. 5.3% of top embryos within trisomies and monosomies $p=0.32$).

Morphological assessment through the embryologist was not possible for all aneuploid embryos on day three and day five, due to earlier occurring degeneration and arrest. The number of assessable embryos is clearly low compared to the total number of embryos analyzed and should be considered when interpreting the results (Table 3).

Some chromosomal aneuploidies did not lead to blastocyst stage embryos, interestingly mostly monosomies affecting chromosomes 1, 3, 4, 7, 18 while all trisomies appeared in blastocyst stage embryos. It must be considered though, that the observed number of embryos is low so the relevance of this outcome must be interpreted critically.

Additionally, some aneuploid constellations seem to have more developmental potential then others. Monosomies 2, 5, 8, 10, 16, 17, 20, 21 and 22 were assessed in morphological

Table 3 Comparing top embryos at day three and in the blastocyst stage within monosomies and trisomies

	Embryos with Monosomies only: 188	Embryos with Trisomies only: 145	*p*-values
Assessable D3 Embryos	77.1% (145/188)	69.6% (101/145)	$p=0.75$
Top Day 3 Embryos	17.6% (33/188)	20% (29/145)	$p=<0.01$
Assessable Blastocysts	28.2% (53/188)	28.3% (41/145)	$p=0.81$
Top Blastocysts	5.3% (10/188)	8.3% (12/145)	$p=0.32$

top blastocysts while monosomies 1, 3, 4, 7,9, 11, 12, 13, 14, 15, 18 and 19 never occurred in top-quality assessed day five embryos.

Trisomies 2, 4, 5, 8, 9, 10, 11, 12, 13, 16, 17, 18 and 20 were found in morphological top-quality blastocysts, embryos while chromosomes 1, 3, 6, 7, 14, 15, 19, 21 and 22 never occurred in top-quality assessed embryos. It is interesting to mention that in trisomy 21, the most common viable aneuploidy, the blastomere rate, as one of the morphological quality criteria, was always so low that it did not result in morphological top-quality embryos at the blastocyst stage. Within the other quality criteria, trisomy 21 embryos performed better, raising the question of how meaningful the individual morphological criteria actually are. A systematic review [11] from 2018 observed the predictive value of morphokinetic parameters to determine embryo ploidy, concluding, that morphologic criteria alone should not be used for aneuploidy screening due to its limited informative value.

We could find a clear age dependent increase of oocytes with more than two chromosomes maldistributed. Most were found among 41-year-old female patients, followed by 42-year old's which is consistent with the literature describing a correlation between female age and frequency of chromosomal abnormalities [12, 13].

Among the combined aneuploidies, chromosomes 15, 16, 21 and 22 were the most affected, just as with single aneuploidies. A plausible explanation could be that chromosomes 15, 16, 21 and 22 may be located close to each other on the meiotic spindle leading to combined nondisjunction.

A closer look at the reasons for natural abortions shows, that in more than 50% a chromosomal abnormality was the cause [14]. All autosomal monosomies and nearly all autosomal trisomies are lethal at embryonic stage. While monosomy X (Ullrich-Turner Syndrome) is the only known viable monosomy, trisomy 18 (Edwards Syndrome) and trisomy 13 (Pätau Syndrome) are the most common trisomies born alive after trisomy 21 (Down Syndrome) [15].

Within aneuploidies of chromosome 15, 16, 21 and 22, trisomy 21 is the only viable chromosomal anomaly, with which affected people can live well into adulthood, depending on its severity and manifestation [16].

Possible consequences of the study

PGT is not performed in all cases of IVF/ICSI, so most embryo transfers follow the assessment of an embryologist choosing top embryos by morphologic parameters.

As seen in this study, a non-negligible proportion of morphological top embryos were genetically aneuploid and thus do not result in a (healthy) pregnancy. It can be concluded from this, that in daily reproductive medicine a certain proportion of aneuploid embryos are transferred unintentionally without previous PGT.

From a medical, psychological, and economic point of view, the question therefore arises whether IVF/ICSI treatment should in principle be preceded by PGT. The price of PGT is generally higher than IVF/ICSI alone, but if the number of required IVF cycles is lower due to the selection of euploid embryos, the physical, psychological, and financial burden is lower than with conventional IVF/ICSI treatment without PGT.

Limitations of the study

The most important limitation of the study to mention is, that this is a retrospective study design which was single center conducted. Although the study included more than 900 oocytes, there is still some selection bias as these patients are not a representative sample for the global population (lack of balanced ethnicity).

Moreover, not all embryos could be observed to the blastocyst stage due to arrest in earlier developmental stages or transfer of single embryos before blastocyst development. Morphological assessment was performed intermittently and not continuously through time-lapse systems.

The aim of this study was to address the impact of meiotically derived maternal aneuploidies on early embryo development. To assess both, maternally and paternally derived aneuploidy, trophectoderm biopsy would have to be performed in combination with polar body biopsy, as polar body biopsy only displays maternally derived aneuploidy.

Conclusion

Individual chromosomal aneuploidies have diverse effects on early embryonic development. Comparing the morphological assessments showed, that the scope of chromosomes to develop into a morphological top blastocyst is wider within trisomies (13 out of 22) than within monosomies (nine out of 22), although overall, embryos with a trisomy do not have a greater potential to develop into a morphological top blastocyst, than embryos with a monosomy.

The primary question of this study, which chromosomal constellations have the possibility and the potential to develop into a morphological top embryo despite chromosomal maldistribution, is answered by monosomies 2, 5, 8, 10, 16, 17, 20, 21 and 22 as well as trisomies 2, 4, 5, 8, 9, 10, 11, 12, 13, 16, 17, 18 and 20.

It can be concluded from this, that morphological evaluation of an embryo is insufficient to select the most suitable embryo for transfer. From this follows, that in daily reproductive medicine a certain proportion of aneuploid embryos is transferred unintentionally without previous PGT, which may lead to decreased pregnancy rates and elevated rates of miscarriage.

Potential source of bias

As this study only examines patient data from a single center providing reproductive medical treatments, potential source of bias are little ethnic diversity and small sample size.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10815-023-02922-9.

Declarations

Conflict of interest None.

References

1. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century. Hum Reprod Update. 2015;21(4):411–26.
2. Gruhn JR, Zielinska AP, Shukla V, Blanshard R, Capalbo A, Cimadomo D, et al. Chromosome errors in human eggs shape natural fertility over reproductive life span. Science. 2019;365(6460):1466–9.
3. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet. 2001;2(4):280–91.
4. Lodge C, Herbert M. Oocyte aneuploidy—more tools to tackle an old problem. Proc Natl Acad Sci. 2020;117(22):11850–2.
5. Schenk M, Groselj-Strele A, Eberhard K, Feldmeier E, Kastelic D, Cerk S, et al. Impact of polar body biopsy on embryo morphokinetics-back to the roots in preimplantation genetic testing? J Assist Reprod Genet. 2018;35(8):1521–8.
6. Verpoest W, Staessen C, Bossuyt PM, Goossens V, Altarescu G, Bonduelle M, et al. Preimplantation genetic testing for aneuploidy by microarray analysis of polar bodies in advanced maternal age: a randomized clinical trial. Hum Reprod. 2018;33(9):1767–76.
7. Feichtinger M, Stopp T, Gobl C, Feichtinger E, Vaccari E, Madel U, et al. Increasing live birth rate by preimplantation genetic screening of pooled polar bodies using array comparative genomic hybridization. PLoS One. 2015;10(5):e0128317.
8. Feichtinger M, Gobl C, Weghofer A, Feichtinger W. Reproductive outcome in European and Middle Eastern/North African patients. Reprod Biomed Online. 2016;33(6):684–9.
9. ESHRE PGT Consortium and SIG-Embryology Biopsy Working Group, Kokkali G, Coticchio G, Bronet F, Celebi C, et al. ESHRE PGT Consortium and SIG Embryology good practice recommendations for polar body and embryo biopsy for PGT. Hum Reprod Open. 2020; 2020(3):hoaa020.
10. Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. Hum Reprod. 2011;26(6):1270–83.
11. Reignier A, Lammers J, Barriere P, Freour T. Can time-lapse parameters predict embryo ploidy? A systematic review. Reprod Biomed Online. 2018;36(4):380–7.
12 Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril. 2014;101(3):656-663 e1.
13. Lam A, Capuzzo M, Imbrogno MG, Donno V, Spedicato GA, Sacchi S, et al. The complex relationship between female age and embryo euploidy. Minerva Obstet Gynecol. 2021;73(1):103–10.
14. Coelho FF, Marques FK, Gonçalves MS, Almeida VC, Mateo EC, Ferreira AC. Detection of aneuploidies in spontaneous abortions by quantitative fluorescent PCR with short tandem repeat markers: a retrospective study. . Genet Mol Res. 2016;23(3):15.
15. Viotti M. Preimplantation Genetic Testing for Chromosomal Abnormalities: Aneuploidy, Mosaicism, and Structural Rearrangements. Genes (Basel). 2020;11(6):602.
16. Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, et al. Down syndrome. Nat Rev Dis Primers. 2020;6(1):9.